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Physical Chemistry in Biology and Medicine

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PREFACE

The writing of this book has been in response to a number of requests, and it is intended for research workers in biology and medicine. It in no way partakes of the nature of a text on all the subjects considered. In seeking training in regular classes the reader may have felt the need of courses in algebra, trigonometry, analytical geometry, calculus, theoretical physics, physical chemistry and physiology, and the study of this book is not intended as a substitute for training in any of these lines. Very often the biologist fails to receive early training which he later feels the need of. Two alternatives are open to him, either to confine his biological studies to phases of the work which do not require the training which he has missed, or to turn back and make good his deficiencies. It is the latter alternative which we wish to encourage.

The advancement of science is partly dependent on the application of the discoveries in one branch to other branches. In order that biology may receive the aid of physics, a number of young physicists have been given positions in biological laboratories where they must spend some years becoming familiar with biology. That is an excellent practice. It is also desirable that the biologist study the mathematical and physical aspects of his subject. For the purpose of acquiring an interest in this line of work the following books are recommended for his study:

Griffin, An Introduction to Mathematical Analysis, New York, 1922.

Granville, Elements of the Differential and Integral Calculus (revised ed.), New York, 1911.

Gibson, An Elementary Treatise on the Calculus, 2d ed., New York, 1906.

Jeans, Theoretical Mechanics, New York, 1907.

Jeans, The Mathematical Theory of Electricity and Magnetism, 4th ed., Cambridge, Eng., 1920.

Millikan, The Electron, 2d ed., Chicago, 1924.

Findlay, Osmotic Pressure, 2d ed., New York, 1919.

Lewis and Randall, Thermodynamics and the Free Energy of Chemical Substances, New York, 1923.

Clark, The Determination of Hydrogen Ions, 2d ed., Baltimore, 1922.

Bancroft, W. D., Applied Colloid Chemistry, New York, 1921.

Bayliss, Principles of General Physiology, 3d ed., New York, 1924.

Lillie, Protoplasmic Action and Nervous Action, Chicago, 1923.

It would be clearly impossible for us to cover the whole field in one volume, and in choosing the subject matter we have included some of the results of our own researches together with those of others on related subjects, and have included other matter which we hope will serve as an introduction.

We have gained a great deal of information from the books listed above as well as from the literature lists at the end of each section and have quoted from Physical Chemistry of Vital Phenomena, by J. F. McClendon, Princeton, 1917.

We wish to thank the following persons for their kindly criticism: Dr. Wilder D. Bancroft, Dr. Frank H. MacDougall, Dr. R. A. Gortner, Prof. Clayton O. Rost, Dr. Elmer J. Lund, Dr. Ella Carter, Dr. Geo. E. Fahr, Dr. D. T. MacDougal, Dr. L. A. Sarver, and Dr. Roger F. Brunel. The English was revised by Geo. C. McClendon.

THE AUTHORS.

MINNEAPOLIS, MINN.,
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ABBREVIATIONS

A	age
a	activity
a	proportionality factor
B	chemical base
b	proportionality factor
C	capacitance in farads
c	concentration
c	constant or proportionality factor
d	derivative
E	electromotive force in volts
E	energy
e	base of natural logarithms
e	electron, charge on electron
F	free energy
F	faraday = 96,500 coulombs
f	frequency (cycles per second)
f	corrected vapor pressure
g	gas
H	heat content
h	increment of V
h	height
I	current in amperes
i	stimulus
K	equilibrium constant
k	dielectric constant
k	constant
L	inductance in henrys
l	liquid
l	length
M	gram molecular concentration
m	mass
m	molality
N	gram equivalent concentration
n	number
n	constant
P	osmotic pressure in atmospheres
p	logarithm of reciprocal
p	gas pressure in atmospheres
q	heat absorbed
R	gas constant

r	radius
r	ratio
S	entropy
s	sensation
s	solid
T	absolute temperature
t	time
t	temperature, centigrade
U	$=\frac{V}{h}$
u	mobility of anions
u	proportionality factor
V	valence
V	volume in liters
v	mobility of cations
v	proportionality factor
W	weight
w	work
w	proportionality factor
X	reactance in ohms
x	co-ordinate of a point
x	unknown quantity
Y	admittance $=\frac{1}{Z}$
y	co-ordinate of a point
Z	impedance in ohms
z	co-ordinate of a point

α	dissociation
β	constant
Γ	excess of solute in surface of solution
γ	surface tension in dynes per centimeter
Δ	freezing-point lowering in degrees centigrade
δ	difference
∂	partial derivative (all but two variables constant)
ε	electric charge on phase
η	viscosity
Λ	equivalent conductance in reciprocal ohms
μ	micron = 0.001 mm.
$\mu\mu$	= 0.000001 mm.
ν	valence
π	ratio of circumference to diameter of a circle
ρ	density
σ	surface in sq. cm.
χ	specific conductivity in reciprocal ohms per centimeter cube.
Ω	resistance in ohms

PHYSICAL CHEMISTRY
IN
BIOLOGY AND MEDICINE

PART I
PHYSICO-CHEMICAL

CHAPTER I

MASS AND VOLUME

Perhaps the most fundamental property of matter is mass, *m*, which is manifested by its inertia when acted upon by a force such as gravitation. When we weigh a body we seek to determine its mass, but we make use of the force of gravitation. The gravitational attraction between two bodies varies directly as the product of the masses of the two bodies, and inversely as the square of the distance between them. When one of the attracting bodies is the earth the gravitational force is called the force of gravity, and the force of gravity upon a body is called the weight of the body. In any given location upon the earth's surface weight is proportional to mass; but whereas the mass of a body is invariable, its weight changes over the surface of the earth on account of the varying distance from the center of the earth. The apparent weight changes also from pole to equator on account of the change in the centrifugal force due to the earth's rotation. The apparent weight is also affected by the buoyancy of the air and a correction must be made for the difference in the weight of air displaced by the body and that displaced by the standard weights used. In order that weight may be expressed quantitatively with the same precision as is used in expressing mass we must adopt certain standard conditions under which the weight is to be determined. It is considered that the weight of a given mass as measured *in vacuo,* at sea level on the 45th parallel of latitude, is numerically equal to its mass.

Since the *mass* of a gram weight does not change with the attraction of gravity or buoyancy of air, it is proper to compare brass weights (for instance) with one another without any precautions as to location or buoyancy of air. The more the volume of the substance weighed differs from the combined volumes of the weights used, the greater the error due to buoyancy of air unless corrections are applied.

The chemical balance for determining weights is essentially a beam having an agate knife-edge pivot in the center resting on an agate plane, and an agate knife-edge at each end on which there rests a plane supporting a pan. If the pivot is not in the center of the beam the weighings will vary by a constant factor. The simplest way to determine this factor is to use standardized weights, and, after placing a large weight on one pan, balance it with weights on the other and determine the ratio of weights in the two pans. If this factor has not been determined it is necessary to weigh the unknown on one pan, then on the other, and if there is a difference, the true weight is the square root of the product of the two weighings. Even though the pivot is in the center of the beam unequal heating of its two ends will expand them unequally and make the weighings incorrect. The expansion is reduced to a minimum if the beam is made of a perfect specimen of invar or fused quartz.

If mere relative differences in weight, and not absolute weights, are desired, the buoyancy of air may be disregarded, but the substance whose change in weight is measured must be at the same temperature on the first and last weighing, as otherwise it would displace a relatively different amount of air by a change in volume. In ordinary chemical work the Centigrade scale of temperature is used.

Air inside of closed containers is weighed, but if it is of the same temperature, pressure, and composition (moisture content) as the outside air, its weight does not need to be considered. A liter of dry air under standard conditions (at 0°, 760 mm. Hg, at sea level, on the 45th parallel) weighs 1.2926 grams.

Perhaps the object of the metric system was the use of a single ultimate standard, the meter, but this object has not been achieved. The kilogram was intended to be the mass of a cubic decimeter of pure water at its maximum density (about 4°). The standard kilogram is not exactly that. The liter is the volume of a kilogram of water at its maximum density, but it is not exactly a cubic decimeter, hence the use of the term milliliter (ml.) for 0.001 liter. The difference between a cubic centimeter (cc.) and a milliliter is too small to be considered in most chemical work since 1 liter equals 1000.027 cc.

Since the bodies of animals consist of over 60 per cent. water, most of the substances in them are in solution. In fact, the study of aqueous solutions will form the major part of the subject of this book. Water is called the solvent and the dissolved substance is called the solute.

As the temperature rises from 4° the density of water decreases. If it is desired to calibrate a liter flask by weighing water in it, it is necessary to boil distilled water to remove the air, cool *in vacuo* to room temperature, fill the flask with it, and weigh. If weighed with brass weights in air, with barometric pressure at 760 mm., relative humidity at 50 per cent., and temperature at 20°, it should weigh 997.18 grams. An error of 5° caused by guessing at the temperature would cause an error of 0.1 per cent. in a calibration. After calibration slight changes in temperature may be disregarded, since 4° change in temperature changes the volume of the flask only 0.01 per cent. In volumetric analysis it is necessary to have the solutions compared at the same temperature.

The unit amount of any chemical substance is the mol, which is the molecular weight expressed in grams. Sometimes after dissolving one mol of a substance in water, dissociation (electrolytic or hydrolytic) may occur and two or more substances be formed, but for convenience we call a solution made by dissolving one mol of a substance in water to make one liter, a molal solution (*M*). The volume of this solution will not remain constant with change in temperature, and such a standard is very awkward where changes of temperature occur; hence the mol fraction (or ratio of mols of solute to total mols in the solution) is a useful method of expression. The standard temperature *in vitro*, when great care is taken to maintain it, is 25°. Of course, processes occurring in the human body take place at a temperature (37°) which is nearly constant, that is to say, there is only a small diurnal variation except at the surface of the body, where greater changes occur.

How temperature and concentration affect density of aqueous solutions is illustrated by sea water. The salinity is expressed as the number of grams of total solids per kilogram of sea water, and hence is not affected by temperature changes. It is determined by titrating the grams of chlorine (contained in the chloride) per kilogram of sea water, and multiplying by a factor. Suppose 20 grams of chlorine per liter were titrated at 30°. The density at this temperature is 1.022. There would then be $20 \div 1.022 = 19.57$ grams of chlorine per kilogram of sea water. This means a salinity of 35. At 4° the density of this sample of sea water would be 1.028.

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THE ATOM

The atom, formerly considered to be an indivisible unit, has recently been subjected to analysis and shown to possess a complex structure of smaller units. The details of this structure are largely hypothetical. According to Bohr's theory the atom resembles a solar system, but G. N. Lewis pictured the outer portion as a series of concentric cubical shells. The following sketch is taken largely from Bohr's theory.

The atom consists of a relatively small electropositive nucleus and one or more hypothetical shells in which are located the orbits of revolution of negative electric charges, electrons (Figs. 1 and 2). These electrons have a mass 1/1845 that of the hydrogen atom, so that most of the mass of an atom is concentrated in the positive charge, *proton;* the actual space occupied by both proton and electron is very small compared with the volume occupied by the atom as a whole, so that atoms and molecules are not solid particles, but are largely empty space. The lightest atom has only one shell and the heaviest has seven. The maximum number of electron orbits that may be contained in the four inner shells are 2, 8, 18 and 32, but the outermost shell never contains more than 8. The electrons, 1 to 8, contained in the outer shell are called valence electrons and determine the group in the periodic system to which the element belongs. The idea of shells is not contained in Bohr's theory, but was proposed by G. N. Lewis. The orbits of one shell may be elliptical and invade the region of another shell.

The atomic nucleus consists of positive electric charges, protons, together with about half as many electrons. In the whole

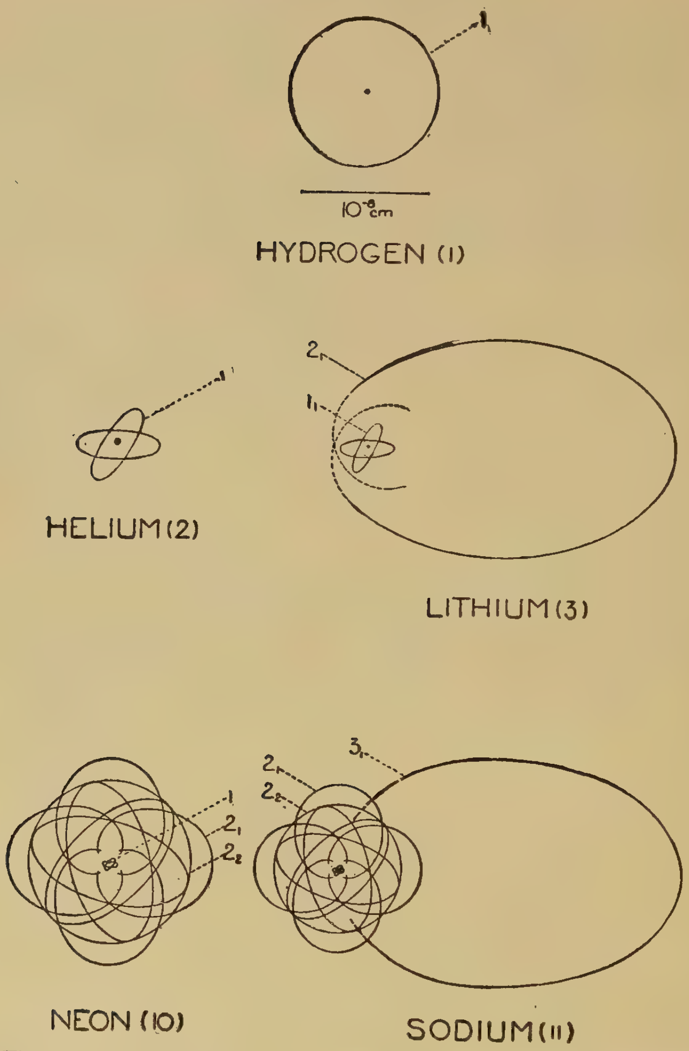
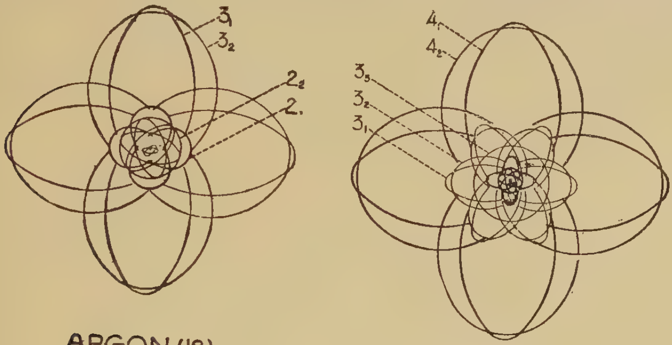


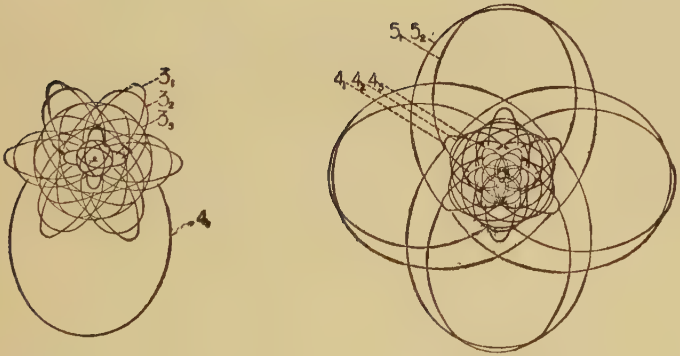
Fig. 1.—The electron orbits of atoms. The nucleus may be considered as a small spot in the center. The numbers refer to the electron orbits and shells in which they lie, thus, 2, refers to the first orbit in the second shell. The outer orbits are of valence electrons. (From Millikan.)

atom the number of protons equals the number of electrons. The number of electrons in the shells of an atom constitutes its atomic number. Since the unit of structure of the atom is one proton plus one electron, the atomic weights are approximate multiples



ARGON (18)

KRYPTON (36)



COPPER (29)

XENON (54)

Fig. 2.—The electron orbits of atoms. The outer orbits are of valence electrons. (From Millikan.)

of the lowest atomic weight, that of hydrogen. An atom of hydrogen consists of one proton forming the nucleus, and one elec-

ATOMIC WEIGHTS

Element.	Atomic number.	Atomic weight.	Isotope weights.	Number of electrons in each shell.
H	1	1.008	1.008	1
He	2	4.00	4	2
Li	3	6.94	7; 6	2; 1
Be	4	9.1	9	2; 2
B	5	10.9	11; 10	2; 3
C	6	12.005	12	
N	7	14.008	14	
O	8	16.000	16	
F	9	19.0	19	
Ne	10	20.2	20; 22	2; 8
Na	11	23.00	23	2; 8; 1
Mg	12	24.32	24; 25; 26	2; 8; 2
Al	13	27.0	27	2; 8; 3
Si	14	28.1	28; 29; (30)	
P	15	31.04	31	
S	16	32.06	32	
Cl	17	35.46	35; 37	
A	18	39.9	40; 36	2; 8; 8
K	19	39.10	39; 41	2; 8; 8; 1
Ca	20	40.07	40; (44)	2; 8; 8; 2
Sc	21	45.1		2; 8; 9; 2
Ti	22	48.1		2; 8; 10; 2
V	23	51		
Cr	24	52		
Mn	25	54.93		
Fe	26	55.84	56; (54)?	
Co	27	58.97		
Ni	28	58.68	58; 60	
Cu	29	63.57		2; 8; 18; 1
Zn	30	65.37	64; 66; 68; 70	2; 8; 18; 2
Ga	31	70.1		2; 8; 18; 3
Ge	32	72.5		
As	33	74.96	75	
Se	34	79.2	80; 78; 76; 82; 77; 74;	
Br	35	79.92	79; 81	
Kr	36	82.92	84; 86; 82; 83; 80; 78	2; 8; 18; 8
Rb	37	85.45	85; 87	2; 8; 18; 8; 1
Sr	38	87.63		2; 8; 18; 8; 2
Yt	39	89.33		2; 8; 18; 9; 2
Zr	40	90.6		2; 8; 18; 10; 2
Cb	41	93.1		
Mo	42	96		
Ru	44	101.7		
Rh	45	102.9		
Pd	46	106.7		
Ag	47	107.88		2; 8; 18; 18; 1
Cd	48	112.40		2; 8; 18; 18; 2
In	49	114.8		2; 8; 18; 18; 3
Sn	50	118.7	120; 118; 116; 124; 119; 117; 122; (121)	
Sb	51	120.2		
Te	52	127.5		
I	53	126.92	127	
Xe	54	130.2	129; 132; 131; 134; 136; 128; 130; (126); (124)	2; 8; 18; 18, 8

Element.	Atomic number.	Atomic weight.	Isotope weights.	Number of electrons in each shell.
Cs	55	132.81	....	2; 8; 18; 18; 8; 1
Ba	56	137.37	....	2; 8; 18; 18; 8; 2
La	57	139	....	2; 8; 18; 18; 9; 2
Ce	58	140.25	....	2; 8; 18; 19; 9; 2
Pr	59	140.9	....	2; 8; 18; 20; 9; 2
Nd	60	144.3		
Sa	62	150.4		
Eu	63	152		
Gd	64	157.3		
Tb	65	159.2		
Dy	66	162.5		
Ho	67	163.5		
Er	68	167.7		
Tm_{I}	69	168.5		
Yb	70	173.5		
Lu	71	175	....	2; 8; 18; 32; 9; 2
Ct	72	......	....	2; 8; 18; 32; 10; 2
Ta	73	181.5		
W	74	184		
Os	76	190.9		
Ir	77	193.1		
Pt	78	195.2		
Au	79	197.2	....	2; 8; 18; 32; 18; 1
Hg	80	200.6	(197–200); 202; 204	2; 8; 18; 32; 18; 2
Tl	81	204	AcC^{II} ThC^{II} Rac^{II} ? 208 210	2; 8; 18; 32; 18; 3
Pb	82	207.2	RaD Ra^{-} AcB ThB Th^{-} Th^{+} 210 206 ? 212 208 208	
Bi	83	208	RaC RaE AcC ThC 214 210 ? 212	
Po	84	210	RaA RaF AcA ThA ThC^{-} 218 210 ? 216 212	
Ru(Nt) (Em)	86	222.4	An Tn .... ? 220	2; 8; 18; 32; 18; 8
Ra	88	226	AcX MsTh_{I} ThX .... ? 228 224	2; 8; 18; 32; 18; 8; 2
Ac	89	?	MsTh_2 228	2; 18; 18; 32; 18; 9; 2
Th	90	232.15	Ux_{I} Io UY RdAc RdTh 234 230 ? ? 228	2; 188; 18; 32; 18; 10; 2
Pa	91	?	Ux_2 234	
U	92	238.2	UI UII 238 234	

tron revolving around the nucleus. Beginning with lithium, a number of elements have been shown not to be pure chemical substances, but mixtures of isotopes. Thus lithium is a mixture of two isotopes with atomic weights 6 and 7. No isotopes of helium have been found, and yet its atomic weight is not exactly a multiple of that of hydrogen. Theories as to the cause of this difference are involved in the electromagnetic theory of mass and cannot be considered here. It is supposed that there are two units of atomic structure—hydrogen atoms and helium atoms. Thus carbon of atomic weight 12 is composed of 3 helium atoms of atomic weight 4.

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CHAPTER II

THE COLLOID PARTICLE

Thomas Graham applied the method of dialysis to the purification of substances. In fact, he compared it in its usefulness to the method of fractional distillation depending on differences in vapor pressure. He divided matter roughly into two classes—those substances that diffuse so slowly that diffusion is not a useful process in their separation, and those that diffuse more or less rapidly. It is possible then to separate those that diffuse with almost immeasurable slowness from all other substances. It is also possible to separate substances which diffuse at different rates by repeating the process and thus increasing the purity of the different fractions. Graham called the substances that diffuse with immeasurable slowness "colloids" because *colla,* meaning glue, was one of these substances. The word "colloid" as used, however, does not apply merely to glue-like substances because many colloidal solutions, unlike glue, have a low viscosity. In fact, it is very difficult to make a sharp distinction between colloids and non-colloidal substances.

As to the substances involved, it is more useful to take the view of Von Wiemarn, that all substances may be reduced to the colloidal state, and hence colloid is considered a *state* of matter and not a division of matter. If any solid substance is added to a solvent in excess of its solubility, a portion of it will remain in the solid state. This excess can then be reduced by various means to any degree of fineness, until the particles are reduced to a specified size, when they are called colloidal particles. Usually each particle consists of a number of molecules, but where molecules are very large, one molecule may possibly constitute a colloidal particle. Some substances may be reduced by grinding in a colloid mill, a high-speed mill in which solid and liquid matter are fed in near the axis, and the solid is ground in the liquid by the action of a number of close-fitting baffles or by the shearing action of close-fitting surfaces moving in opposite directions. If the solid is ground in the liquid, a mud or plastic mass may result. The particles in this mud may be of various sizes. As the particles are reduced in size they tend to separate more from one another, and usually are found to be electrically charged. Finally they may reach such a small size that they will stay suspended in the liquid for a very long time, in which case they form a colloidal solution or sol.

If the electric charges are neutralized, as by the action of ions of the opposite sign, the particles may form aggregations which finally may precipitate by their own weight. Colloidal solutions (sols) that act in this way are called *lyophobic colloids*, since they have very little affinity for the liquid, or, as it is sometimes called, the "solvent." There is another class of colloids that will not precipitate even when their electric charges are neutralized. This may be due to the fact that they have a greater affinity for the solvent. Such colloids are called *lyophilic colloids*. Since in the living body water is usually the liquid or solvent, we may speak of *hydrophobic* and *hydrophilic colloids*. Most of the colloids in the living organisms are of the hydrophilic type, but they may be changed over by certain agents to hydrophobic types. At any rate they may be changed so that they will precipitate on neutralization of their electric charges, as in boiling a dilute albumin solution.

The question of what gives the electric charge to the colloidal particle has been very much discussed without any agreement being reached. In fact, it may be different in different cases. The union of a solid or colloidal substance with a molecule or ion in true solution has been defined as adsorption. Adsorption may in some cases bear a similarity to chemical union. For instance, silver ions in true solution may unite with chlorine ions to form silver chloride, which may precipitate if the solubility product is exceeded. Now if we take a colloidal solution of silver, the molecule of silver on the surface of the colloidal particle may unite with the chlorine ion. It then may be said that the colloidal particle has adsorbed the chlorine ion and thus received an electric charge.

Another instance is that of ferric hydroxide sols. When ferric hydroxide is in solution, although it is very poorly soluble, it dissociates into positively charged ferric ions and negatively charged hydroxyl ions. It is therefore possible to assume that on the surface of the colloidal particle of ferric hydroxide some dissociation takes place, giving off hydroxyl ions and leaving the particle positively charged. Or it may be supposed that ferric chloride, which may be in the solution at the same time (and may be present in the colloidal particle as an impurity), dissociates, and that the ferric ion is adsorbed while the chloride ion is not. Or again, it may even be assumed that the ferric chloride is hydrolyzed, giving rise to ferric hydroxide and hydrochloric acid, and that the hydrogen ion is adsorbed while the chloride ion is not, thus giving the particle the positive charge. Space does not allow us to consider these hydrophobic colloids at length. We must now pass on to the hydrophilic colloids.

HYDROPHILIC COLLOIDS

On the basis of weight the greatest amount of hydrophilic colloid in the body is protein. The molecule of protein, with its molecular weight of about 30,000 or more, is large enough to show colloidal properties when the molecules are separate in solution, *i. e.*, a single molecule is as large as some of the colloidal particles in a gold sol, for instance. These proteins, at least many of them, have been crystallized, but the crystals themselves show some colloidal properties, such as colloidal swelling.

Besides the sol a colloid may form a gel, which is an elastic solid consisting of colloidal particles and solvent, or, as it is more conveniently termed, dispersion medium. Since the gel has the character of a solid and yet consists of two phases, one solid and one liquid, it must show a structure. It is not possible to see the colloidal particle through the ordinary microscope, as its diameter is much less than half the wave length of visible light, but some particles (especially of lyophobic colloids) may be brought into evidence by means of the ultramicroscope. The principle of the ultramicroscope is that the colloidal particle, although much smaller than half the wave length of light, is able to change the direction of some of this light—*i. e.*, to scatter the light. The scattered light, then, may be determined by looking from the side. In other words, the ultramicroscope is one in which a powerful beam of light passes through the sol or gel at an angle to the line of vision. The colloidal particles then look like stars against a black sky. They may be colored because of the fact that they scatter light of only certain wave lengths, but their size cannot be determined except very roughly by the amount or by the wave length of light scattered. Some particles scatter light so that the beam of light from an individual particle may be apprehended in the microscope. These are submicrons. Other particles scatter light, and yet within a given magnification the light from the individual particle may not be distinguished separately, but a diffuse illumination from a number of particles may produce an effect such as we get from looking at the Milky Way. It should be remembered, however, that larger particles out of focus may produce the same effect.

The particles are in rapid motion due to their bombardment by the molecules of the dispersing medium (Brownian movement). But when gel formation takes place the particles aggregate in one way or another and their motion is greatly decreased or stopped altogether. It seems that they sometimes aggregate in long chains which unite into a sponge-work, but at other times they form masses of small crystals. In fact, there are many ways of aggregation. The structure may vary after the first gelation has taken place and an amorphous gel may change into a crystalline gel.

With the hydrophilic colloids the structure is very difficult to ascertain with the ultramicroscope. Even in the sol stage the colloidal particles may not scatter enough light for the particles to be separately apprehended. Perhaps all molecules scatter some light; for instance, pure water scatters light, and thus we have the blue color of the sea because it is the blue light that is scattered. Many protein sols or even gels seem to be as clear as water under the ultramicroscope, and yet, with a change of temperature or other conditions, submicrons may appear. When only a few submicrons are present they must be regarded with suspicion, as they may be impurities. The weight of impurity necessary to give a brilliant field in the ultramicroscope is very small. In fact, these impurities may come off from the walls of the container, since colloidal silica may come off from glass containers and colloidal metals from metal containers. Many proteins contain considerable ash (other than phosphoric or sulphuric acid, which are derived from integral parts of the protein). The ash is evidence of impurities. The ash may or may not give rise to visible submicrons.

Owing to the fact that the ultramicroscope reveals so little of the structure of hydrophilic colloids found in organisms, the structure of protein gels is to a large extent hypothetical. One phenomenon made use of in the study of the structure of protein gels is the "weeping" of some gels either under ordinary conditions or under high pressure. In this case the gel is separated into the clot and the serum. The clot is found to contain a relatively high percentage of protein and a low percentage of water, and the serum a relatively low percentage of protein and a high percentage of water. For this reason Ostwald supposed that protein sols were composed of liquid colloidal particles or droplets containing a high percentage of protein and a low percentage of water, suspended as an emulsion in water containing a relatively low percentage of true dissolved protein. It has been shown by Sörensen, however, that some protein sols behave as true solutions to the extent that the observed osmotic pressure may be calculated as though the molecules of protein are individually separated. Perhaps they maintain colloidal properties owing to their enormous size. When gel formation occurs aggregation must take place. This aggregation may continue until a spongework or other continuous structure is built up. Not all the protein molecules, however, are aggregated, and it may be these non-aggregated molecules that are squeezed out of the clot and float in the serum.

Protein is made up of amino-acids attached together by union between the carboxyl group and the amino group, with the elimination of water. Amino-acids have both acidic and basic properties. The carboxyl group gives the amino-acid an acidic character similar to formic acid, and the amino group gives it a basic character similar to simple amines; in fact, they are derived from amines by the replacement of a terminal hydrogen by the radical containing the carboxyl group. This substitution may reduce, but does not prevent, manifestation of the basic character by the amine. An ammonia molecule may combine with a hydrogen ion and receive a positive charge and the amino group of an amino-acid may behave similarly. It has not been clearly shown to what extent proteins behave as amino-acids. The large protein molecule probably offers considerable surface on which adsorption may take place.

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CHAPTER III

INTERMOLECULAR FORCES

OSMOTIC MEMBRANES

Even such colloidal membranes as collodion contain pores, as shown by Bartell and by Duclaux and Errera. The properties of an osmotic membrane depend on the size of the pores and the character of the walls of the pores. About the only characteristic of the walls of the pores that has been extensively studied is the electric charge. An electronegative membrane tends to repel anions and an electropositive membrane to repel cations. For ordinary osmotic effects it is shown by Bigelow and Bartell that the size of the pores in the membrane should be about 0.1 μ or less in diameter, where μ represents micron or 0.001 mm.

If the pores are about 0.2 μ we have a very leaky membrane. If the walls are charged negatively negative (as well as positive) ions may pass through the pores, and if the negative ion is more rapid than the positive ion the dilute side of the solution becomes electronegative. The water filling the pores is charged positively by induction from the negative walls and is dragged through the pores by the electrostatic charge on the dilute side of the membrane. This is what is called negative osmose. A perpetual motion machine is not represented by this process, because this is a leaky membrane and an equalization of the concentration of the solute on the two sides finally occurs.

If the pores are 0.1 μ in diameter and the membrane charged negatively the negative charges on the walls of the pores are too close together to allow a negative ion to pass between, and the negative ion is repelled by the charges. Such a membrane shows no negative osmose, but is a leaky membrane showing the ordinary osmotic effect. If the pore diameter is still further reduced the membrane intercepts smaller and smaller molecules of solute until, finally, all solute molecules are prevented from passing. In some such membranes hydrogen ions may pass and perhaps hydroxyl ions.

Besides the electric charge some other properties of the walls of the pores seem to affect the passage of compounds of large molecules. For instance, alcohol will pass through rubber membranes whose pores are so small that they do not allow the passage of such small particles as the ions of the salts of the alkali metals. It is usually stated that alcohol passes because it dissolves in rubber, but this is merely stating the problem in other words. It may be the shape of the pores or regional arrangements of electric charges on the walls of the pores that allows passage of some substances and not of others. Alcohol causes rubber to swell and the pores to be enlarged.

THE RELATION OF GAS PRESSURE TO OSMOTIC PRESSURE

The simplest state of a chemical substance for the study of energy relations is the gas. Considered from a rough quantitative standpoint most gases approach a state of the perfect gas, the energy of which is a function of the absolute temperature alone and which obeys the equation:

$$\mathrm{p}V = nRT$$

where p (pressure) is expressed in atmospheres, V (volume) in liters, n is the number of mols, T is the absolute temperature in degrees, and R is the gas constant in work per degree. Under standard conditions

If $\mathrm{p} = 1$ and $T = 273.1$
$n = 1,\ V = 22.412$
and therefore $R = 0.08207$

If the number of mols is assumed to be 1, the equation becomes

$$\mathrm{p}V = RT$$

The absolute temperature scale is made by considering the change in volume of a perfect gas at constant pressure with change in temperature. Since the volume of a perfect gas would be zero at absolute zero, any gas would have to liquefy or solidify before reaching absolute zero, and therefore would be very different from a perfect gas. The absolute zero is −273.1° on the Centigrade scale as measured on the gas thermometer corrected for the imperfections of the gas.

From the equation above it follows that the increase in volume of the perfect gas with increase in temperature is proportional to the temperature on the absolute scale.

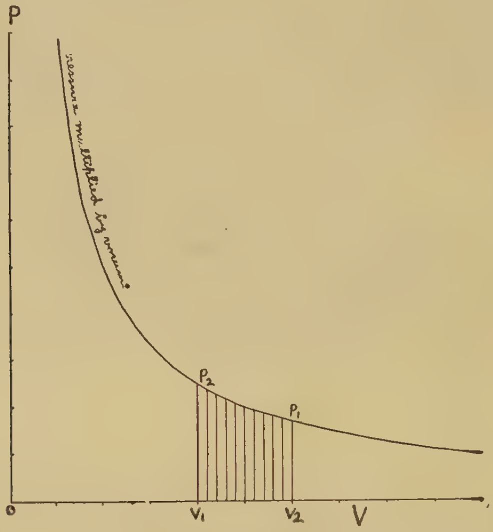

Fig. 3.—Pressure – volume curve (isotherm) of an ideal gas in which the pressure and volume vary in a reciprocal manner. If the pressure is varied from p_1 to p_2 the volume varies from V_1 to V_2.

Since RT is a constant at any given temperature, the volume at that temperature is inversely proportional to the pressure as shown in the curve of the accompanying Fig. 3. Suppose we desire to know the work the gas can do in expanding isothermally from V_1 to V_2, the pressure changing consequently from p_2 to p_1. In Fig. 3 the work done is equal to the area of the surface, V_1V_2-p_2p_1. It is difficult to estimate this area at once because one side is bounded by a curved line, so we cut it up by vertical lines into a series of approximate rectangles of varying length. These lines may be imagined as being so close together that the change of volume in passing from one rectangle to the next is infinitesimal, and the change in pressure therefore negligible. Each change in volume is represented by δV, the corresponding fraction of the work done by $p\delta V$, and the total work (w), or the sum of all the small rectangles, by

$$w = \int_{V_1}^{V_2} p\delta V \qquad (1)$$

This expression must be gotten into a practical form, the first step being to multiply and divide by V, hence

$$w = \int_{V_1}^{V_2} \frac{pV\delta V}{V}$$

But since pV is a constant, it may be omitted from the summation process (integration) and introduced again afterward, hence

$$w = pV \int_{V_1}^{V_2} \frac{\delta V}{V}$$

Since for one mol of a gas, the following equation applies:

$$pV = RT$$

it follows that

$$w = RT \int_{V_1}^{V_2} \frac{\delta V}{V} \qquad (2)$$

It can also be shown that

$$\frac{\delta V}{V} = \delta(\log_e V)$$

where δ ($\log_e V$) means the change in value of $\log_e V$ when V changes a very small amount, δV, which may be represented by h.

Let

$$y = \log_e V$$

and

$$y_1 = \log_e (V + h)$$

then

$$y_1 - y = \log_e (V + h) - \log_e V$$

and

$$\frac{y_1 - y}{h} = \frac{\log_e (V + h) - \log_e V}{h}$$

$$= \frac{1}{h} \log_e \frac{V + h}{V}$$

$$= \frac{1}{h} \log_e \left(1 + \frac{h}{V}\right)$$

but

$$y_1 - y = \delta (\log_e V)$$

and

$$h = \delta V$$

hence

$$\frac{\delta (\log_e V)}{\delta V} = \frac{1}{h} \log_e \left(1 + \frac{h}{V}\right) \qquad (3)$$

In order to facilitate calculation, let

$$U = \frac{V}{h}$$

therefore

$$\frac{1}{U} = \frac{h}{V}$$

and

$$\frac{1}{h} = \frac{U}{V}$$

By substitution in (3)

$$\frac{1}{h} \log_e \left(1 + \frac{h}{V}\right) = \frac{1}{V} U \log_e \left(1 + \frac{1}{U}\right)$$

$$= \frac{1}{V} \log_e \left(1 + \frac{1}{U}\right)^U \qquad (4)$$

Since

$$\frac{1}{h} = \frac{U}{V}$$

U increases as h decreases; and h becomes vanishingly small as U becomes infinitely large. Hence, by the binomial theorem,

$$\left(1+\frac{1}{U}\right)^{U}=1+\frac{U}{1}\cdot\frac{1}{U}+\frac{U\,(U-1)}{2\,.\,1}\cdot\frac{1}{U^2}\cdots\cdots$$

$$=1+\frac{1}{1!}\cdots\cdots=2.71828=e$$

Hence, from equations (3) and (4)

$$\frac{\delta\,(\log_e V)}{\delta V}=\frac{1}{V}\log_e e$$

But

$$\log_e e=1$$

hence

$$\frac{\delta\,(\log_e V)}{\delta V}=\frac{1}{V}$$

and

$$\delta\,(\log_e V)=\frac{\delta V}{V} \qquad (5)$$

Substituting (5) in (2) we obtain:

$$w=RT\,(\log_e V_2-\log_e V_1)$$

$$w=RT\left(\log_e\frac{V_2}{V_1}\right) \qquad (6)$$

Since p and V are inversely proportional, the equation may also be written

$$w=RT\left(\log_e\frac{p_1}{p_2}\right) \qquad (7)$$

As is well known, work may be obtained from the steam engine, as indicated in Equation 1. In the cylinder of the steam engine work on the piston is performed by expansion of the gas, and δV expresses the change in volume due to expansion of the gas. If the units for p and V are atmospheres and liters, R (as in Equation 7) is then in terms of liter-atmospheres per degree.

If p is dynes per sq. cm. and V is cc., R is expressed in ergs per degree. Since a joule $= 10^7$ ergs, and a liter-atmosphere $= 101.33$ joules and 1 gram calorie $= 4.183$ joules, it is possible to transform one unit of work into another by changing the value of R (since R expresses work per degree).

When expressed in liter-atmospheres per degree, $R = 0.08207$; when expressed in joules per degree, $R = 8.316$; when expressed in gram calories per degree, $R = 1.9885$.

Since all forms of energy may be transformed into heat it is well to know the relation of the calorie (the unit of heat) to other energy units. The small or gram calorie is the heat required to raise the temperature of 1 gram of water 1°. This amount varies slightly with change in temperature and the standard temperature is from 15° to 16°.

It was shown by Van't Hoff that there is a similarity between the osmotic pressure of an ideal solution and the hypothetical gas pressure, supposing the solute were in the form of a perfect gas occupying the same volume as the solution. Actual gases do not obey the gas laws exactly unless corrections are applied for the space occupied by the molecules and for molecular attraction (Van der Waals). Similar relations hold for solutions, but are complicated by the fact that solvation reduces the amount of the solvent and increases the space occupied by the solute and, furthermore, ionization may occur to a far greater extent in polar solvents than in gases. Ionization alters the attraction between particles of the solute (Debye). With these qualifications, osmotic pressure P may be substituted for gas pressure, p, in Equation 7, and we obtain

$$w = R\,T \log_e \frac{P_1}{P_2} \qquad (8)$$

H. N. Morse constructed very strong clay cups and connected them with nitrogen manometers, and in this way measured the osmotic pressure of sugar solutions placed in the cup. Copper ferrocyanide membranes are impermeable to sugar molecules and to some salts, such as magnesium sulphate, but they are injured by contact with potassium chloride and some other salts. It is, therefore, very difficult to determine the osmotic pressure of these salts.

According to Morse each sugar molecule combines with 6 molecules of water when dissolved in this solvent. With the molecules of such enormous size as we meet in living matter the space occupied by the molecules is very great, and hence the divergence from the simple equation is very great. The osmotic pressure of a 30 per cent. gum arabic solution is 4 atmospheres, whereas that of a 60 per cent. solution is 48 atmospheres.

The relation of vapor pressure to osmotic pressure is illustrated by the following example:

If a solid body is dissolved in a liquid, the vapor pressure of the solution is less than that of the pure solvent. For instance, if we have under an evacuated bell jar a beaker of pure water and a beaker of water in which cane-sugar has been dissolved, the vapor pressure of the pure water is greater than that of the cane-sugar solution and water will evaporate from the pure water and will condense on the cane-sugar solution. This process will continue until all of the pure water is evaporated and passed into the cane-sugar solution. On the other hand, if under a tall evacuated bell jar we place a beaker of cane-sugar solution at the top and the pure water at the bottom, as the pure water evaporates and condenses in the cane-sugar solution the latter will be diluted, and finally a condition of equilibrium will be established whereby the difference in vapor pressure of the two liquids will be exactly counterbalanced by the difference in pressure of water vapor upon their surfaces (due to the weight of the column of vapor) and no more change will take place.

The relation between the lowering of vapor pressure of a solvent and the concentration of the solute is expressed by Raoult's law, which states that in an ideal solution,

$$\frac{p_1 - p_2}{p_1} = \frac{n}{n_1 + n} \text{ (the mol fraction)}$$

when p_1 and p_2 denote the vapor pressure of the solvent in the pure state and in the solution, and n_1 and n the number of mols of solvent and solute respectively. Where the solution is very dilute the number of mols of solute is negligible in comparison with the number of mols of solvent, and Raoult's equation may be written

$$\frac{p_1 - p_2}{p_1} = \frac{n}{n_1}$$

Since from the formula $P\,V = n\,R\,T$ it may be seen that

$$n = \frac{P\,V}{R\,T}$$

Hence Raoult's formula may be written

$$\frac{p_1 - p_2}{p_1} = \frac{P V}{n_1 R T}$$

and the osmotic pressure, P, of an ideal solution may be calculated from the relative lowering of the vapor pressure:

$$P = \frac{p_1 - p_2}{p_1} \times \frac{n_1 R T}{V}$$

In order to calculate the concentration from the osmotic pressure corrections have to be applied for the volume occupied by the molecules of the solute and for molecular attraction. The result of the calculation without these corrections does not represent concentration. For that reason the term "activity" is used. In employing the term "activity" no assumptions are made as to its real significance—it is a function by which predictions may be made of the work substances in solution can do. As we shall see in the following chapters activity is used in estimation of electromotive force as well as of osmotic work, whereas these cannot be predicted from their concentration.

Direct determinations of osmotic pressure are difficult. Freezing-point determinations are more easily performed than determinations of vapor pressure, and osmotic pressure may be calculated from depression of the freezing-point of the solution.

The relation of the activity of the solute to the lowering (Δ) of the freezing-point of the solvent produced by the presence of the solute is expressed in the equation:

$$d \log_e a = \frac{d \Delta}{1.858}$$

Since the activity, a, may be calculated also from the osmotic pressure, the osmotic pressure may be calculated from the freezing-point. The equation is

$$P = 12.06 \Delta - 0.021 \Delta^2$$

The following table by Harris and Gortner gives values of osmotic pressure for various values of Δ.

TABLE OF OSMOTIC PRESSURES IN ATMOSPHERES FOR DEPRESSION OF THE FREEZING POINT $P = 12.060\Delta - .021\Delta^2$

Δ °	Hundredths of degrees, centigrade									
	0	1	2	3	4	5	6	7	8	9
0.0	0.000	0.121	0.241	0.362	0.482	0.603	0.724	0.844	0.965	1.085
0.1	1.206	1.327	1.447	1.568	1.688	1.809	1.930	2.050	2.171	2.291
0.2	2.412	2.532	2.652	2.772	2.893	3.014	3.134	3.255	3.375	3.496
0.3	3.616	3.737	3.857	3.978	4.098	4.219	4.339	4.459	4.580	4.700
0.4	4.821	4.941	5.062	5.182	5.302	5.423	5.543	5.664	5.784	5.904
0.5	6.025	6.145	6.266	6.386	6.506	6.627	6.747	6.867	6.988	7.108
0.6	7.229	7.349	7.469	7.590	7.710	7.830	7.951	8.071	8.191	8.312
0.7	8.432	8.552	8.672	8.793	8.913	9.033	9.154	9.274	9.394	9.514
0.8	9.635	9.755	9.875	9.995	10.12	10.24	10.36	10.48	10.60	10.72
0.9	10.84	10.96	11.08	11.20	11.32	11.44	11.56	11.68	11.80	11.92
1.0	12.04	12.16	12.28	12.40	12.52	12.64	12.76	12.88	13.00	13.12
1.1	13.24	13.36	13.48	13.60	13.72	13.84	13.96	14.08	14.20	14.32
1.2	14.44	14.56	14.68	14.80	14.92	15.04	15.16	15.28	15.40	15.52
1.3	15.64	15.76	15.88	16.00	16.12	16.24	16.36	16.48	16.60	16.72
1.4	16.84	16.96	17.08	17.20	17.32	17.44	17.56	17.68	17.80	17.92
1.5	18.04	18.16	18.28	18.40	18.52	18.64	18.76	18.88	19.00	19.12
1.6	19.24	19.36	19.48	19.60	19.72	19.84	19.96	20.08	20.20	20.32
1.7	20.44	20.56	20.68	20.80	20.92	21.04	21.16	21.28	21.40	21.52
1.8	21.64	21.76	21.88	22.00	22.12	22.24	22.36	22.48	22.60	22.72
1.9	22.84	22.96	23.08	23.20	23.32	23.44	23.56	23.68	23.80	23.92
2.0	24.04	24.16	24.28	24.40	24.52	24.63	24.75	24.87	24.99	25.11
2.1	25.23	25.35	25.47	25.59	25.71	25.83	25.95	26.07	26.19	26.31
2.2	26.43	26.55	26.67	26.79	26.91	27.03	27.15	27.27	27.39	27.51
2.3	27.63	27.75	27.87	27.99	28.11	28.23	28.34	28.46	28.58	28.70
2.4	28.82	28.94	29.06	29.18	29.30	29.42	29.54	29.66	29.78	29.90
2.5	30.02	30.14	30.26	30.38	30.50	30.62	30.74	30.86	30.98	31.09
2.6	31.21	31.33	31.45	31.57	31.69	31.81	31.93	32.05	32.17	32.29
2.7	32.41	32.53	32.65	32.77	32.89	33.00	33.13	33.25	33.36	33.48
2.8	33.60	33.72	33.84	33.96	34.08	34.20	34.31	34.43	34.56	34.68
2.9	34.79	34.91	35.04	35.16	35.27	35.39	35.51	35.63	35.75	35.87
3.0	35.99	36.11	36.23	36.35	36.47	36.59	36.71	36.83	36.95	37.06
3.1	37.18	37.30	37.42	37.54	37.66	37.78	37.90	38.02	38.14	38.26
3.2	38.38	38.50	38.62	38.73	38.85	38.97	39.09	39.21	39.33	39.45
3.3	39.57	39.69	39.81	39.93	40.05	40.17	40.28	40.40	40.52	40.64
3.4	40.76	40.88	41.00	41.12	41.24	41.36	41.48	41.60	41.71	41.83
3.5	41.95	42.07	42.19	42.31	42.43	42.55	42.67	42.79	42.91	43.02
3.6	43.14	43.26	43.38	43.50	43.62	43.74	43.86	43.98	44.10	44.22
3.7	44.33	44.45	44.57	44.69	44.81	44.93	45.05	45.17	45.29	45.41
3.8	45.52	45.64	45.76	45.88	46.00	46.12	46.24	46.36	46.48	46.60
3.9	46.71	46.83	46.95	47.07	47.19	47.31	47.43	47.55	47.67	47.79
4.0	47.90	48.02	48.14	48.26	48.38	48.50	48.62	48.74	48.86	48.97
4.1	49.09	49.21	49.33	49.45	49.57	49.69	49.81	49.93	50.04	50.16
4.2	50.28	50.40	50.52	50.64	50.76	50.88	50.99	51.11	51.23	51.35
4.3	51.47	51.59	51.71	51.83	51.94	52.06	52.18	52.30	52.42	52.54
4.4	52.66	52.78	52.89	53.01	53.13	53.25	53.37	53.49	53.61	53.73
4.5	53.84	53.96	54.08	54.20	54.32	54.44	54.56	54.68	54.79	54.91
4.6	55.03	55.15	55.27	55.39	55.51	55.62	55.74	55.86	55.98	56.10
4.7	56.22	56.34	56.46	56.57	56.69	56.81	56.93	57.05	57.17	57.29
4.8	57.40	57.52	57.64	57.76	57.88	58.00	58.12	58.23	58.35	58.47
4.9	58.59	58.71	58.83	58.95	59.06	59.18	59.30	59.42	59.54	59.66
5.0	59.78	59.89	60.01	60.13	60.25	60.37	60.49	60.60	60.72	60.84
5.1	60.96	61.08	61.20	61.32	61.43	61.55	61.67	61.79	61.91	62.03
5.2	62.14	62.26	62.38	62.50	62.62	62.74	62.85	62.97	63.09	63.21
5.3	63.33	63.45	63.56	63.68	63.80	63.92	64.04	64.16	64.27	64.39
5.4	64.51	64.63	64.75	64.87	64.98	65.10	65.22	65.34	65.46	65.58
5.5	65.69	65.81	65.93	66.05	66.17	66.29	66.40	66.52	66.64	66.76
5.6	66.88	67.00	67.11	67.23	67.35	67.47	67.59	67.71	67.82	67.94
5.7	68.06	68.18	68.30	68.41	68.53	68.65	68.77	68.89	69.01	69.12
5.8	69.24	69.36	69.48	69.60	69.71	69.83	69.95	70.07	70.19	70.30
5.9	70.42	70.54	70.66	70.78	70.90	71.01	71.13	71.25	71.37	71.49

In biological laboratories water is always the solvent, and hence the freezing-point thermometer may have the zero set at 0°. In this case, however, it must be graduated in one hundredths of a degree from 0° to $-5°$. Strictly speaking, the thermometer should be immersed in the solution up to the top of the mercury column. This is not practical, however, and measurements depend on having certain lengths of it at the temperature of the solution and another more or less uniform length at the temperature of the room, which should be constant. Under these constant conditions a zero point is obtained by the freezing of freshly boiled distilled water. When the temperature of a solution is lowered it may reach several degrees below the freezing-point before freezing occurs. Freezing may be initiated by the dropping in of a small crystal of ice. It is more convenient to freeze water in the hollow of a glass bead and drop in the bead at the right moment, because a crystal of ice usually melts on the surface and sticks. Usually mercury may not wet glass, but this is due to a film of air, which may be absent in the thermometer. When the mercury column is contracted it seems to stick, at least in places, to the glass, and the adhesion may cause the column to break, in which case a true reading cannot be made. If the stem of the thermometer is tapped frequently with a cork mallet while the mercury is contracting such adhesions may be broken loose. In order to obtain correct results the whole solution to be frozen must be at the same temperature. To insure this, conduction of heat by the solution is not depended upon, but it is stirred by means of a loop of wire which is raised and lowered. This stirring, however, is not sufficient if the heat is escaping rapidly and irregularly, therefore the solution is surrounded by a relatively poor conducting layer, such as air or alcohol. The complete apparatus consists of a pail of ice containing a large test-tube in which is inserted a smaller test-tube containing the solution and the thermometer. Perforated stoppers are inserted so that the thermometer does not touch the small test-tube and the small test-tube does not touch the large test-tube. The hole in the inner stopper admits a wire for stirring and the side neck on the inner test-tube admits the glass bead containing the crystal of ice. In order to bring about freezing salt must be added to the ice in the pail, and this must be stirred with a large wire loop. When many determinations are made it is convenient to use ether in place of the ice and obtain the freezing by evaporating the ether with a blast of air. If alcohol separates the two test-tubes, the freezing of the solution may be observed directly through the apparatus. Alcohol conducts heat too rapidly to be used in case the freezing mixture is salt and ice unless the temperature of the freezing mixture is properly adjusted.

Ordinarily the behavior of the mercury column indicates the moment of freezing. After the solution is cooled the mercury contracts, but if any supercooling occurs freezing is accompanied by an expansion of the mercury, and the temperature of the solution rises rapidly until the true freezing-point is reached; then it may drop slowly because of further cooling. Under these conditions the true freezing-point of the solution is never observed. For instance, suppose we had a molecular solution of sugar and supercooling occurred to such an extent that when freezing was initiated half of the water froze before the solution was warmed to the freezing-point; this freezing-point is then that of a 2 *M* solution. This is an exaggerated case, but considerable error may arise from such a source. Therefore Harry C. Jones calculated the correction to be applied to the freezing-point. If a cubic centimeter of water is cooled one degree below its freezing-point one small calorie of heat is given out, but if 1 cc. of water freezes 80 calories of heat are given out. Therefore, if one degree of supercooling occurs the first sudden freezing concentrates the solution 1/80 and by subtracting 1/80 of the observed Δ for every degree of supercooling the true depression of the freezing-point is supposed to be obtained.

More accurate determinations may be made by means of a thermocouple. The junction of the thermocouple is immersed in the solution to be frozen, and the two free ends are joined to copper wires and the joints immersed in melting ice in a Dewar flask. An accurate, low resistance potentiometer is used in measuring electromotive force.

A factor modifying the osmotic properties of substances in solution is their unequal distribution on two sides of a semipermeable membrane according to Donnan's equation for membrane equilibria. When a membrane separates solutions of two electrolytes with a common ion, one electrolyte of which can diffuse through the membrane while the other contains an ion that cannot, there results an unequal distribution of the diffusible ions on the two sides of the membrane.

Suppose two electrolytes, Na AcO (1) and R AcO (2), are separated by a membrane permeable to Na^+ and AcO^-, but not to R^+. The Na AcO diffuses through the membrane to the opposite side (2), where some of the dissociated R^+ and AcO^- recombine to form undissociated R AcO. Although Na^+ must be present in smaller amounts than AcO^- in the solution to which they have diffused (2), Na^+ and AcO^- must necessarily be equal in concentration in the solution from which diffusion took place (1).

If we express the activity of the molecules and ions by brackets, when equilibrium has been established:

$$[Na^+{}_1] = [Acet^-{}_1] \tag{9}$$

and

$$[Acet^-{}_2] = [Na^+{}_2] + [R^+{}_2] \tag{10}$$

when dn mols. of NaAcO (Na^+ and AcO^-) have been transferred from (1) to (2) the work done equals zero, and

$$dn\ RT \log_e \frac{[Na^+{}_1]}{[Na^+{}_2]} + dn\ RT \log_e \frac{[AcO^-{}_1]}{[AcO^-{}_2]} = 0$$

and hence

$$[Na^+{}_1] \times [AcO^-{}_1] = [Na^+{}_2] \times [AcO^-{}_2] \tag{11}$$

Substituting (9) and (10) in (11) we obtain:

$$(Na^+{}_1)^2 = [Na^+{}_2] \times ([Na^+{}_2] + [R^+{}_2])$$

Therefore the activity of the Na ion is finally unequal on the two sides of the membrane. Donnan has given the following illustration: When the activity of the non-diffusible ion, R^+, is unity and the activity of the diffusible ion (Na^+) is 0.001, the activity of the diffusible ion in (1) is (at equilibrium) 99 per cent. of its initial activity.

SURFACE TENSION

The surface of a pure liquid or solution is in a state of tension called surface tension, which is explained by the unsymmetric arrangement of the forces between molecules, there being no molecules outside the surface to compensate for the attraction of the molecules inside the surface. Fischer observed oil films on mercury 5 $\mu\mu$ thick, where 1 $\mu\mu$ is a millionth of a millimeter. Lord Rayleigh (1899) observed that an oil film 1 $\mu\mu$ thick on water lowered the surface tension. Hatschek estimated the thickness of the adsorbed water film on particles of colloidal sulphur to be 0.87 $\mu\mu$. The double film of a soap-bubble may be as thin as 5 $\mu\mu$.

The diameters of molecules are, according to Perrin (1910), H_2, 0.2 $\mu\mu$; He, 0.17; O_2, 0.26; N_2, 0.27; Cl_2, 0.4, and hence some films are not many molecules thick. The tension developed, however, is considerable, that on the surface of water being about 75 dynes per centimeter. This causes small drops of water to round up into approximate spheres. The surface tension changes with the curvature of the surface and a small drop will distil into a large body of the same liquid. Surface energy is equal to the area of the surface multiplied by the surface tension.

J. Willard Gibbs showed that it is a general rule that substances that lower the surface tension of a solvent become more concentrated in the surface film than in the interior. When equilibrium is reached the concentration of the adsorbed substance in the surface may be calculated by the formula

$$\Gamma = -\frac{c}{RT}\,\frac{d\gamma}{dc}$$

where Γ equals the excess of solute in the surface layer above that in the solution, c the concentration of the solute, and γ the surface tension. When $\frac{d\gamma}{dc}$ is positive (*i. e.*, when the solute increases the surface tension of the system) Γ is negative (*i. e.*, there is a movement of solute away from the surface), and when Γ is positive the solute accumulates in the surface.

Some substances slightly raise the surface tension of the solvent (but never to nearly so great an extent as substances of the other class may lower the tension). They also tend to be driven out of the surface film. The surface tension of the surface between the solvent and a vacuum is not the same as that between the solvent and some other liquid or solid phase. Surface tension is more easily measured in the surface between air and liquid. This is almost the same as that between a vacuum and the liquid. An absolute vacuum cannot be obtained owing to the vapor tension of the liquid.

Surface tension is measured by the force required to pull a ring or plate from the surface of a liquid or by the pull of a suspended drop of the liquid (the force equals the weight of the drop at the moment it falls), or by the rise of the liquid in a capillary tube of known bore made of a material that is wetted by the liquid, or by the force required to blow a bubble of air from the mouth of a capillary tube into the liquid. The material of the walls of the capillary makes no difference provided it is wetted by the solvent, in which case it is covered by a layer of adsorbed solvent. Much work has been done to determine the angle of contact, but this is really in all cases zero because of the presence of the adsorbed film (Bancroft). Liquids that do not wet the walls of the capillary not only do not rise in the tube, but are depressed by it. In this case there is a layer of adsorbed air between the liquid and the tube. If this air is driven out, the liquid may wet the tube.

The most common method of measuring surface tension is the drop weight method, and the drop may be weighed or its weight may be calculated from the volume of the drop and its specific gravity. In biological laboratories aqueous solutions are those usually investigated, and since the surface tension of pure water is known the surface tension of any solution is compared with that of pure water by comparing the weight of a drop of pure water with that of the weight of a drop of solution. Since substances that lower the surface tension of water collect in the surface and since time is required for this process the age of the drop when it falls is important. A different result is obtained when the drops follow in rapid succession from that obtained when they fall more slowly. In fact, this aging goes on for minutes and perhaps hours, but the greatest changes occur in the first second, and for approximate measurements a drop a minute or so old will give nearly the final values. The size of the surface from which the drop falls makes a difference in the calculations. The dropping surface should not be very different from 5 mm. in diameter. In order that the same area of surface is wetted each time the end of the tube is ground off at right angles to its length and polished. If the drop is to be weighed some arrangements must be made to slow up the formation of the drop and to prevent evaporation of the drop after it falls. The drop may be measured in a graduated pipet by reading the heights between the fall of two drops or the average height between the fall of the first drop and, say, the hundredth drop, and the weight calculated from the specific gravity.

ADSORPTION

The concentration in the surface of substances that lower the surface tension of the solvent is sometimes called adsorption. This is often studied on the surface between a solid and a liquid, and the substance is said to be adsorbed by the solid, but in the same way substances may be adsorbed by air-bubbles in the solution or on the surface of oil droplets in water.

The adsorbed substance may form a continuous layer of molecules, and if this layer is of a solid substance there will form a solid film on the surface. Sometimes a second layer may be built on the first, and in this way a membrane may be built up. Langmuir, Harkins, and others have shown that these molecules may be polarized in regard to the surface, the polar (carboxyl) group of a fatty acid molecule extending into the water and the non-polar (hydrocarbon) portion extending into the oil. According to

Manley a film of air 20 molecules thick is retained by glass in high vacua.

The nature of adsorption is a matter of discussion. Many quantitative experiments on adsorption have been brought as evidence that adsorption is not chemical combination. Adsorption depends on the concentration of the adsorbed substance, but is not a linear function. In fact, it approaches a logarithmic function up to adsorption saturation, when the surface will not adsorb any more. If the adsorption is plotted against the concentration on cartesian co-ordinates the curve approaches a logarithmic curve. Low concentrations cause relatively greater adsorption than do higher concentrations. Since the temperature must be kept constant the curve is called the adsorption isotherm. The formula for the curve is

$$x^n = kc$$

where x is the amount adsorbed per unit of adsorbing surface, c is the concentration, and n and k are constants that are different for different temperatures and substances. Geddes (1909) found $n = 1.77$ for the adsorption of CO_2 gas by charcoal at 31° where c is in terms of mm. Hg pressure and $x =$ cc. CO_2 per cc. charcoal and $k = 0.0602$. Reychler (1910) found $n = 1$ where c is in same terms, but $x =$ millimols of CO_2 per gram of blood charcoal at 20° and $k = 0.00024$. In adsorption from aqueous solution $n = 1$–10.

Adsorption is a factor in the formation of emulsions. Many solutes have long been known to aid in emulsification and to stabilize emulsions. In regard to two liquids, as oil and water, it has been shown that some solutes aid in the formation of an emulsion of oil in water, and others aid in the formation of an emulsion of water in oil. It was shown by Clowes that whereas sodium soaps favor the emulsion of oil in water, calcium soaps favor the emulsion of water in oil. In this way the addition of calcium may help to invert an emulsion or change a "wet" one into an "oily" one. It was shown by Harkins that this is due to the fact that the adsorbed soap molecules are polarized with respect to the surface. The long carbon chains extend into the oil, but the ends attached to the sodium or calcium extend into the water. The molecule is wedge-shaped or pyramidal and these wedges are put together in the form of an arch or dome. If the oil end of the wedge is the larger, an emulsion of water in oil occurs, and if the water end is the larger, an emulsion of oil in water occurs. Since calcium combines with two fatty acid molecules the size of the oil end of the molecule is doubled and inverts the emulsion. There may be considered two surface tensions, one of the oil-soap surface and one of the soap-water surface. An inequality of these surface tensions would affect the stability of the emulsion.

It has been suggested by Langmuir that in some cases adsorption may be simply a chemical union of a layer of solute molecules to the surface layer of molecules of the substance on which it is adsorbed (adsorbent). In other cases, however, this seems not to be true. Often a surface adsorbs ions of the charge opposite to the charge on the surface. In the case of many organic compounds of large molecules it appears that they are not particularly attracted by the adsorbent, but they are driven out of the solution and have no other place to go.

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CHAPTER IV

ELECTROLYTIC DISSOCIATION AND CHEMICAL EQUILIBRIA

ELECTROLYTIC DISSOCIATION

Certain substances when dissolved in polar solvents dissociate to a large extent into electrically charged ions, and are therefore called electrolytes, to distinguish them from poorly dissociated, so-called non-electrolytes such as sugar or urea. In gases individual ions may be detected, but in solutions we are usually content with the circumstantial evidence of their existence. In biology we nearly always have to deal with aqueous solutions, and these are implied where others are not stated. Electrolytes that dissociate to a great extent in water ionize much less, if at all, in non-aqueous solutions. Water is a highly polar solvent, a fact which accounts for its high dielectric constant and ionizing power. The electrostatic attraction between a positive and negative ion placed at the distance by which they are separated in solution would be very great (when calculated by the law of inverse squares, assuming a vacuum between the ions). The high dielectric constant of the water separating the ions may be the condition which makes their continued separate existence possible. Elements which form ions have incomplete outer shells of electrons—usually less than 8 valence electrons (Figs. 1 and 2).

In general we may divide electrolytes into two classes—the strong and the weak. Strong electrolytes are dissociated to a great extent, whereas weak electrolytes are dissociated to a very small extent. So-called "non-electrolytes" may be dissociated to a minute extent. Water is a very weak electrolyte. Its ions are the most rapid, but it is poorly dissociated. Although the concentration of water is about 55 mols to the liter, only 10^{-7} mols in a liter are dissociated at about 22°.

The behavior of strong acids and bases and their salts has been accounted for by assuming that dissociation increases with dilution until they are completely dissociated at infinite dilution. According to Debye they are always completely dissociated. Although weak acids and bases and their salts are, as a rule, poorly dissociated, salts formed of a weak acid and a strong base or a weak base and a strong acid are hydrolyzed and dissociated. The ordinary inorganic acids and bases are strong, and organic weak, but there are exceptions.

Solutions of all chlorides contain Cl ions. NaCl dissociates into positively charged Na ions (Na^+) and negatively charged Cl ions (Cl^-). Since the atoms of elementary Na and Cl are electrically neutral and yet NaCl dissociates into electrically charged ions, it is assumed that in NaCl one electron in excess of the neutral atomic supply is held by the Cl and the supply for Na is deficient in one electron. The ions are always hydrated.

It should be emphasized that strong electrolytes exist chiefly as ions in the dilute solutions with which we have to deal in biochemistry. Take, for example, the neutralization of HCl with KOH. Since HCl, KOH, and KCl are highly dissociated the reaction becomes $H^+ + OH^- = H_2O$. Cl^- and K^+ are present in about the same quantities before and after the reaction takes place. That the reaction is simply the formation of water from its ions is illustrated by the fact that no matter what strong base or acid is substituted for those named above, at 20°, 13,700 gram calories of heat are produced for each gram equivalent of acid and alkali used.

ELECTRIC CONDUCTIVITY OF AQUEOUS SOLUTIONS

Solutions of electrolytes conduct the electric current and are called conductors of the second class to distinguish them from metals, which are conductors of the first class. If an electric current is passed through a solution from two metallic conductors (electrodes) the positive ions (cations) migrate to the negative electrode (cathode) and the negative ions (anions) migrate to the positive electrode (anode). The greater the number of ions there are in a solution, the greater the electrical conductivity, hence the electrical conductivity (conductance ratio) may be used to show qualitatively the ionization. The mobility of the ions influences conductivity. Hydration of ions and increased viscosity of solution slightly reduce mobility.

The electrical resistance in ohms is measured and the conductivity is the reciprocal of the resistance.

If we attempt to pass an electric current through a solution from metallic electrodes, a considerable difference in potential (of the order of magnitude of 1 volt) is necessary in order to accomplish the oxidation and reduction at the electrodes, and this counterelectromotive force at the electrodes impedes the current and is called polarization. Furthermore, if much current is passed in one direction, the resistance at the electrodes is variable because of resistance of gas bubbles and it is impossible to determine the electric conductivity of the solution. If, however, not enough difference of potential is maintained to accomplish the oxidation and reduction, the phase boundary between the electrode and the solution will act as an electric condenser and the current will flow until the condenser is charged. This condenser action (condensance or condensive reactance) opposes the current. By a suitable set-up of apparatus this reactance may be eliminated. In this way the electric conductivity of the solution may be measured and the concentration of ions in it calculated.

Suppose we take an electric-conductivity-cell with two parallel plates. The plates separated by air will act as an air condenser. We may measure the capacity of this condenser by means of a suitable set-up, using an alternating current. If we then fill it with an aqueous salt solution its capacity enormously increases. It now acts as two condensers coupled in series with each other and with a resistance (that of the salt solution). One electrode and the solution touching it acts as a condenser with plates very close together and connected by a conductor, the solution, with the other condenser. If, instead of the solution, we fill the cell with pure air-free water, its capacity is less than with salt solution, but about 80 times as great as with air. In this case the slight conductivity of the water may be eliminated in calculating the result. The undissociated water molecules have an effect in increasing the capacity of the condenser, possibly because of the conductivity within the molecule itself. That is to say, when placed in an electric field, each water molecule may possibly become positive at one end and negative at the other —*i. e.*, polarized. These polarized molecules may become so arranged in the electric field as to form numerous condensers arranged in series, stretching from one electrode to the other and giving water the high dielectric constant it is known to possess. Freezing reduces the dielectric constant.

The polarity of the water molecules, responsible for its high dielectric constant, is probably the cause of the great ionization of electrolytes in aqueous solution. Ions may possibly unite with water molecules by means of these regional differences in potential.

Gram and others have determined the current, I, in amperes passing through the electrolyte while the electromotive force, E, in volts remains constant. In order to reduce polarization, the transient current (the current immediately after closing the circuit) is measured. The resistance, Ω, is calculated from Ohm's law:

$$\Omega = \frac{E}{I}$$

Very accurate measurements cannot be made by this method, as the current is changing and never reaches a constant value so long as the circuit contains electrolytes as well as metallic conductors, because of polarization at the electrodes. Newbery obviated this difficulty by the use of so-called non-polarizable electrodes such as calomel electrodes. The resistance of the calomel electrodes is slightly variable and is in series with that of the solution whose resistance is to be measured. Therefore, Newberry did not measure the total resistance, but calculated the resistance of the solution in question, using a value for E obtained by tapping the electrolytic conductor at two points a measured distance apart by means of two additional calomel electrodes connected with an instrument for determining the difference of potential in volts.

The electrical resistance is usually determined by means of the Kohlrausch alternating current method. The solution to be examined is placed in a conductivity cell which consists of a glass vessel containing two electrodes. The electrodes are made of platinum or gold plates and should stand vertically so that bubbles will not collect on them. If the distance between the electrodes is changed to the slightest degree, the cell has to be standardized again. To avoid this the gold or platinum is often made thick for stiffness and protected by the walls of the vessel, or the four corners of one electrode are connected to the corners of the other by means of glass rods fused to the electrodes by heat. To the upper edge of the gold or platinum plate a stout platinum wire is welded. This is done by heating platinum plate and wire to white heat and welding the wire to the plate by means of a quick tap with a hammer. When gold is used a gold bead is fused to the end of the wire and then hammered into the form of a plate. The platinum should be cleaned by heating it to a white heat and dipping it in hydrochloric acid, then reheated. The wire is fused into the junction of the conductivity vessel with a small glass tube and a drop of mercury dropped into the tube so as to touch the platinum wire. When connecting the apparatus a copper wire is inserted down the tube into the mercury. The pipet form of conductivity cell is the most convenient for solutions.

Before using the cell it must be cleaned with cleaning fluid made by grinding sodium bichromate in concentrated sulphuric acid. The electrodes may be allowed to remain bright, or they may be roughened to increase the surface. To roughen them the cell is filled with about 2 per cent. solution of platinic chloride containing a trace of basic lead acetate. An electric current of about 4 volts is passed through the cell until one electrode is blackened, and the current is reversed until the other pole is blackened. The platinizing solution is returned to the bottle and the cell rinsed and filled with dilute sulphuric acid. A current is now passed first in one direction and then in the other as before. In this way hydrogen is produced, first on one electrode and then on the other, and any chlorine that may have been absorbed by the platinum is reduced. The cell is now rinsed many times, finally with conductivity water, is filled with the latter, and left until used. Conductivity water is made by adding sulphuric acid and potassium bichromate to distilled water and redistilling it, then adding barium hydroxide to it, and distilling it the third time. During the third distillation CO_2 is excluded by incomplete condensation, some steam being allowed to escape out of the collecting vessel. The use of conductivity water is not always necessary, and distilled water boiled fifteen minutes may be substituted.

Since one degree rise in temperature results in an increase in electric conductivity of about 2.5 per cent., the conductivity cell must be placed in a water-bath or oil-bath the temperature of which is kept constant, or at least observed very accurately at the moment of determination. If the electrodes are 1 cm. apart and if each electrode surface as well as the cross-section of the vessel between them be 1 sq. cm., the conductivity of the solution in reciprocal ohms is the specific conductivity (χ). The usual practice is not to measure the electrodes, but to calibrate the cell with a solution of potassium chloride of known concentration, the conductivity of which is taken from tables. The specific conductivity multiplied by 1000 and divided by the concentration in gram equivalents per liter is called the equivalent conductivity (Λ). It is found that the equivalent conductivity of an electrolyte increases with dilution possibly because the dissociation increases. At infinite dilution the dissociation would be complete and is practically complete at 0.0001 M. The equivalent conductivity at infinite dilution is extrapolated and is denoted by $\Lambda_\circ$. $\Lambda/\Lambda_\circ$ is the conductance ratio.

If a solution of weak electrolyte is diluted with pure water the increase in equivalent conductivity may be calculated by means of the formula:

$$\mathrm{M}\ \frac{(\Lambda/\Lambda_\circ)^2}{1 - \Lambda/\Lambda_\circ} = K$$

This equation does not hold for strong electrolytes. According to Debye strong electrolytes are completely dissociated in a solution of any concentration. He supposes that the attraction between positive and negative ions in concentrated solutions exerts a force opposed to the electric current. Hence the decrease of electric conductivity in very concentrated solutions of some electrolytes, such as sulphuric acid, does not necessarily indicate a lower concentration of ions in such solutions.

If a continuous current is passed from electrodes through a solution the ions that carry the current through the solution accumulate at the electrodes and give up their electric charges with the inauguration of certain chemical reactions. This changes the composition of the solution. In order to prevent this change an alternating current is used in measuring the electrical conductivity of a solution. Such a current of 60 cycles per second may be obtained from the lighting circuit. Rapidly alternating currents of pure sine wave form may be obtained from the Vreeland oscillator. Electron tube oscillators usually produce one or more harmonics. The frequency of the alternations should not change during a set of measurements because this changes the impedance of the circuit.

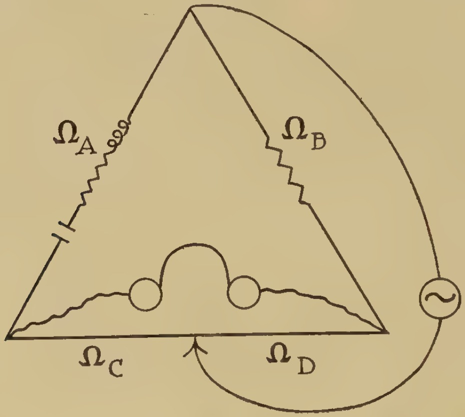

Fig. 4.—Wheatstone bridge arrangement for electric conductivity with alternating current. A standard resistance is used, Ω_B. The solution to be investigated is placed in a conductivity electrode vessel which is represented by Ω_A, but which has a capacity reactance (capacitance) which is balanaced out by series coupling with a variometer, represented by the coils in the wire. The ratio of Ω_C to Ω_D may be varied by moving the sliding contact represented by the arrow point. The bridge is balanced by determining the point at which there is silence in the head phones. The circle to the right represents an alternate current generator.

A Wheatstone bridge (Fig. 4) may be built up of a resistance box or other form of standard resistance Ω_B, the conductivity vessel Ω_A, a meter resistance wire Ω_{CD} with a sliding contact and a telephone which connects the junction of Ω_A and Ω_C with the junction of Ω_B and Ω_D. The meter wire is divided by the sliding contact into two resistances, Ω_C and Ω_D. The two secondary poles of the induction coil or other source of current are connected one to the sliding contact and the other to the juncture between the cell Ω_A and the box Ω_B. The current entering the circuit at the juncture of Ω_A and Ω_B divides, part going through Ω_A and Ω_C, and the other part through Ω_B and Ω_D. If the two ends of the meter wire have the same electric potential as indicated by silence in the telephone, then:

$$\frac{\Omega_A}{\Omega_B} = \frac{\Omega_C}{\Omega_D} \text{ and } \frac{\Omega_A}{\Omega_C} = \frac{\Omega_B}{\Omega_D}$$

Even though the resistances are balanced, if there is any speeding up or retarding of the alternations in one unit of the bridge, the potential at the two ends of the meter wire will not be the same at the same time. This time element is associated with the reactance, X, of the circuit, and where the reactance enters the sum total of obstacles to the current is called the impedance, which is the square root of the sum of the squares of the resistance and the reactance. Since the reactance, $X = 2\,\pi f\,L - \frac{1}{2\,\pi f C}$ we obtain the equation:

$$Z = \sqrt{\Omega^2 + \left(2\,\pi f\,L - \frac{1}{2\,\pi f\,C}\right)^2}$$

where Z is the impedance; Ω, the resistance in ohms; f, the cycles per second; L, the inductance in henrys, and C, the capacitance in farads. Since the two halves of the meter wire Ω_C and Ω_D are necessarily the same, or nearly the same in reactance, a simple method for making the time element the same at the two ends of the meter wire is to have the reactance the same in unit Ω_A as it is in unit Ω_B, in which it is negligible. (The reactance is composed of the inductance and capacitance according to the above formula.) Resistance boxes with negligible inductance and capacitance can be obtained from makers of radio apparatus. The trouble lies in the conductivity vessels. In passing a rapidly alternating current through a conductivity vessel filled with a solution of electrolytes, no current passes between the electrodes and the solution. The surface of the electrode acts as a condenser. When the metal electrode is charged positively, the solution nearest to it is charged negatively, and vice versa. This condenser has a very high capacitance owing to the extremely narrow distance between the two "plates," that is, the surface of the metal and the surface of the solution. The greater the surface of the metal, the greater the capacitance of the condenser, and hence roughening the surface increases the capacitance. The conductivity vessel contains theoretically two condensers connected in series and in series with a resistance which is the solution. Since the reactance X is equal to $2 \pi f L - \frac{1}{2 \pi f C}$, if the frequency remains constant the reactance will equal zero if the proper values of the inductance, L, and the capacitance, C, are taken. If a variometer (a double coil, the inductance of which may be varied) is placed in series with the conductivity vessel the inductance may be varied until the reactance is zero in Ω_A. The method of using the variometer is as follows: Slide the sliding contact on the meter wire until the feeblest tone is heard in the telephone. Then turn the knob of the variometer until the tone is still further lowered. Now move the slide wire until a new tone-minimum is reached and adjust the variometer again, repeating this until silence in the telephone results. It may be necessary to ground the sliding contact or some other point in the circuit. The electric resistance of the variometer does not change by turning the knob, and hence, in making the calculations, the resistance of the variometer is marked down as a constant figure in ohms. The resistance of the box is read in ohms. The resistances of the two parts of the meter wire may not be known, but are proportional to their lengths, and hence their lengths are used in the equation. From the equation:

$$\frac{\Omega_A}{\Omega_B} = \frac{\Omega_C}{\Omega_D}$$

the resistance, Ω_A, may be calculated. The resistance of the conductivity cell is the resistance, Ω_A, minus the resistance of the variometer. The ratio of the two parts of the meter wire $\frac{\Omega_C}{\Omega_D}$ may be read from the accompanying table:

.100's	10's	UNITS									
		0	1	2	3	4	5	6	7	8	9
	0	.00 0000	1001	2004	3010	4016	5025	6036	7049	8064	9082
	1	.0 1010	1112	1214	1317	1420	1523	1626	1730	1833	1937
	2	.0 2041	2145	2250	2354	2459	2564	2670	2775	2881	2987
	3	.0 3093	3199	3306	3413	3520	3627	3735	3843	3950	4058
	4	.0 4167	4275	4384	4493	4602	4712	4820	4931	5042	5152
	5	.0 5263	5374	5485	5596	5708	5820	5932	6044	6156	6269
	6	.0 6383	6496	6610	6724	6838	6952	7066	7180	7296	7412
	7	.0 7527	7643	7759	7875	7992	8109	8225	8342	8460	8578
	8	.0 8696	8814	8933	9051	9170	9290	9408	9528	9649	9770
	9	.0 9890	.1001	.1013	.1025	.1037	.1050	.1062	.1074	.1086	.1099
1	0	.1111	.1123	.1136	.1148	.1160	.1173	.1186	.1198	.1211	.1223
1	1	.1236	.1248	.1261	.1274	.1287	.1300	.1312	.1325	.1338	.1351
1	2	.1364	.1377	.1390	.1403	.1416	.1429	.1442	.1455	.1468	.1481
1	3	.1494	.1507	.1521	.1534	.1547	.1561	.1574	.1587	.1601	.1615
1	4	.1628	.1641	.1655	.1669	.1682	.1695	.1710	.1723	.1737	.1751
1	5	.1765	.1778	.1792	.1806	.1821	.1834	.1848	.1862	.1876	.1890
1	6	.1905	.1919	.1933	.1947	.1962	.1976	.1990	.2005	.2019	.2034
1	7	.2048	.2063	.2077	.2092	.2106	.2121	.2136	.2151	.2165	.2180
1	8	.2195	.2210	.2225	.2240	.2255	.2270	.2285	.2300	.2315	.2331
1	9	.2346	.2361	.2376	.2392	.2407	.2423	.2438	.2454	.2469	.2485
2	0	.2500	.2516	.2532	.2547	.2563	.2579	.2595	.2610	.2625	.2642
2	1	.2658	.2674	.2690	.2706	.2722	.2739	.2755	.2772	.2788	.2804
2	2	.2820	.2837	.2853	.2870	.2887	.2903	.2920	.2937	.2954	.2971
2	3	.2987	.3004	.3020	.3038	.3055	.3072	.3089	.3106	.3123	.3140
2	4	.3157	.3175	.3192	.3210	.3228	.3245	.3262	.3280	.3298	.3316
2	5	.3333	.3351	.3369	.3387	.3405	.3423	.3440	.3459	.3477	.3495
2	6	.3513	.3532	.3550	.3568	.3587	.3606	.3624	.3643	.3662	.3681
2	7	.3699	.3717	.3736	.3755	.3774	.3793	.3812	.3831	.3850	.3869
2	8	.3889	.3908	.3928	.3947	.3966	.3986	.4005	.4024	.4044	.4064
2	9	.4084	.4104	.4124	.4144	.4164	.4185	.4205	.4225	.4245	.4265
3	0	.4285	.4306	.4326	.4347	.4368	.4389	.4409	.4430	.4450	.4471
3	1	.4493	.4514	.4535	.4556	.4577	.4598	.4619	.4640	.4661	.4683
3	2	.4705	.4727	.4749	.4771	.4793	.4814	.4836	.4858	.4881	.4903
3	3	.4925	.4947	.4969	.4992	.5015	.5038	.5060	.5083	.5106	.5129
3	4	.5152	.5174	.5197	.5220	.5244	.5267	5290	.5313	.5336	.5360
3	5	.5384	.5407	.5431	.5455	.5480	.5504	.5528	.5553	.5576	.5600
3	6	.5625	.5650	.5674	.5698	.5723	.5748	.5773	.5798	.5823	.5848
3	7	.5873	.5899	.5924	.5949	.5974	.6000	.6025	.6051	.6077	.6103
3	8	.6129	.6155	.6181	.6207	.6233	6260	.6286	.6313	.6340	.6367
3	9	.6394	.6420	.6447	.6474	.6502	.6529	.6557	.6584	.6611	.6638
4	0	.6666	.6694	.6722	.6750	.6778	.6806	.6834	.6862	.6891	.6920
4	1	.6949	.6978	.7007	.7036	.7065	.7094	7123	7152	.7181	.7211
4	2	.7241	.7271	.7301	.7331	7361	.7391	7421	.7451	.7482	.7512
4	3	7543	.7574	.7605	.7636	7667	.7698	.7729	7760	7792	.7824
4	4	.7857	.7889	.7921	.7953	.7986	.8018	.8050	.8084	.8117	.8150
4	5	.8182	.8215	.8248	.8282	.8316	.8349	.8382	.8416	.8450	.8484
4	6	.8518	.8552	.8586	.8620	.8655	.8691	.8727	.8762	.8798	.8834
4	7	.8868	.8904	.8939	.8975	.9011	.9048	.9084	.9120	.9157	.9194
4	8	.9231	.9267	.9304	.9341	.9379	.9417	.9454	.9493	.9531	.9570
4	9	.9609	.9649	.9687	.9725	.9764	.9803	.9842	.9881	.9920	.9960

100's	10's	UNITS									
		0	1	2	3	4	5	6	7	8	9
5	0	1.000	1.004	1.008	1.012	1.016	1.020	1.024	1.028	1.032	1.036
5	1	1.041	1.045	1.049	1.053	1.058	1.062	1.066	1.071	1.075	1.079
5	2	1.083	1.088	1.092	1.097	1.101	1.105	1.110	1.114	1.119	1.123
5	3	1.128	1.132	1.137	1.141	1.146	1.151	1.155	1.160	1.165	1.169
5	4	1.174	1.179	1.183	1.188	1.193	1.198	1.203	1.208	1.212	1.217
5	5	1.222	1.227	1.232	1.237	1.242	1.247	1.252	1.257	1.262	1.267
5	6	1.273	1.278	1.283	1.288	1.294	1.299	1.304	1.309	1.314	1.320
5	7	1.326	1.331	1.336	1.342	1.347	1.353	1.359	1.364	1.370	1.375
5	8	1.381	1.386	1.392	1.398	1.404	1.410	1.415	1.421	1.427	1.433
5	9	1.439	1.445	1.451	1.457	1 463	1.469	1.475	1.481	1.487	1.494
6	0	1.500	1.506	1.513	1.519	1.525	1.531	1.538	1.544	1.551	1.557
6	1	1.564	1.571	1.577	1.584	1.591	1.597	1.604	1.611	1.618	1.625
6	2	1.632	1.639	1.645	1.652	1.659	1.667	1.674	1.681	1.688	1.695
6	3	1.703	1.710	1.717	1.724	1.732	1.740	1.747	1.755	1.763	1.770
6	4	1.778	1.786	1.793	1.801	1.809	1 817	1.825	1.833	1.841	1.849
6	5	1.857	1.865	1.873	1.082	1.890	1 899	1.907	1.916	1.924	1.933
6	6	1.941	1.950	1.958	1.967	1.976	1.985	1.994	2.003	2.012	2.021
6	7	2.030	2.039	2.048	2.058	2.068	2.078	2.087	2.096	2.106	2.115
6	8	2.125	2.135	2.145	2.155	2.165	2.175	2.185	2.195	2.205	2.215
6	9	2.225	2.236	2.247	2.257	2.268	2.278	2.289	2.300	2.311	2.322
7	0	2.333	2.344	2.355	2.367	2.378	2.389	2.401	2.413	2.425	2.436
7	1	2.448	2.460	2.472	2.485	2.497	2.509	2.521	2.534	2.546	2.559
7	2	2.571	2.584	2.597	2.610	2.623	2.636	2.650	2.663	2.676	2.690
7	3	2.703	2.716	2.731	2.745	2.759	2.774	2.788	2.802	2.817	2.831
7	4	2.846	2.861	2.876	2.891	2.907	2.922	2.937	2.953	2.968	2.984
7	5	3.000	3.016	3.032	3.049	3.065	3.081	3.098	3.115	3.132	3.150
7	6	3.168	3.185	3.202	3.220	3.237	3.255	3.273	3.291	3.310	3.329
7	7	3.348	3 367	3.386	3.405	3.425	3.445	3.464	3.484	3.505	3.525
7	8	3.546	3.566	3 587	3.608	3.630	3.652	3.674	3.695	3.717	3.740
7	9	3.762	3.785	3 808	3.831	3.854	3.878	3.902	3.926	3.950	3.975
8	0	4.000	4.025	4.050	4.075	4 102	4 127	4 154	4 181	4.209	4.236
8	1	4 263	4.290	4.319	4.348	4.376	4 405	4.435	4.464	4.494	4.525
8	2	4 556	4.587	4.618	4.650	4.682	4.715	4.748	4.781	4.814	4.848
8	3	4.882	4.917	4.953	4.988	5.025	5.061	5.097	5.135	5.173	5.211
8	4	5.250	5.290	5.330	5.370	5.411	5.451	5.493	5.536	5.580	5.623
8	5	5.666	5.711	5.757	5.803	5.850	5.898	5.945	5.994	6.043	6.093
8	6	6 143	6.194	6.247	6.300	6.353	6 407	6 463	6 519	6.576	6.634
8	7	6.693	6.752	8.812	6.873	6.937	7.000	7 064	7 129	7.196	7.264
8	8	7.334	7.403	7.474	7.546	7.620	7.696	7 772	7.849	7.928	8.009
8	9	8.091	8.175	8.259	8.346	8.434	8.524	8 616	8.709	8.804	8.901
9	0	9.000	9.101	9.204	9.309	9.416	9.526	9.638	9.753	9.870	9.989
9	1	10.11	10.23	10.36	10.49	10.63	10.76	10.90	11.05	11.19	11.34
9	2	11.50	11.66	11.82	11.99	12.16	12.33	12 51	12.70	12.89	13.08
9	3	13.28	13.49	13.71	13.93	14.15	14.38	14 62	14.87	15.13	15.40
9	4	15.66	15.95	16.24	16.54	16.86	17.18	17 52	17.87	18.23	18.61
9	5	19.00	19.41	19.83	20.28	20.75	21 22	21 73	22.26	22.81	23.38
9	6	24.00	24.64	25.32	26.03	26.77	27 57	28 41	29.30	30.25	31.26
9	7	32.33	33.49	34 70	36.04	37.46	39 00	40.67	42.48	44.44	46.62
9	8	49.00	51.63	54.55	57.83	61.50	65.67	70.43	75.93	82.33	89.91
9	9	99.00	110.1	124.0	141.9	165 7	199.0	249.0	332 3	499.0	999.0

In the practical working of the apparatus there are many points in the construction which cannot be entered into here. The telephone should be a good radio head set. The inductance of the resistance box may be reduced by having each resistance of two wires wound in parallel in opposite directions on a thin sheet of mica, Ayrton-Perry winding, or the resistance may be perfectly straight, such as a thin film of platinum on a quartz fiber. It should be noted that the frequency enters into the formula for the reactance and that high frequencies are preferable in some work. An alternating current galvanometer, or a rectifier, such as a crystal detector or vacuum tube detector, and direct current galvanometer, may be substituted for the telephone.

It is not possible to obtain a frequency higher than about 4000 alternations per second with a Vreeland oscillator. For high-frequency currents it is necessary to use an electron tube oscillator. An electron tube consists of an evacuated glass bulb with a filament like a Mazda lamp, and, in addition, a metallic plate, and, between the plate and filament, a metallic grid. When the filament is heated by an electric current, electrons are given off. If the plate is made electropositive, the electrons are attracted to the plate and thus the current is carried in one direction. Since no electrons are given off by the cold plate, the current cannot pass in the opposite direction and the apparatus acts like a valve. The grid is for the purpose of controlling the valve action. If the grid is charged positively some electrons are caught by it, but others pass through the holes in the grid and reach the plate and a current passes. When the grid is charged negatively, the electrons are driven back to the filament and no current passes. In order to produce an alternating current of, say, a million cycles, it is necessary to alternate the charge on the grid a million times a second, which will produce a pulsating plate current of a million cycles. By passing this current through a coil connected inductively with an independent circuit, an alternating current of a million cycles is produced in the independent circuit in the same way that an alternating current is produced in the secondary circuit of an induction coil. The apparatus is so arranged that it works automatically. Just as a tuning-fork, after receiving a blow, vibrates automatically at a certain frequency, the electron tube oscillator, after receiving a "blow" due to the closing of the switch, oscillates automatically at the frequency of its resonance. Electric resonance depends on the reduction of the reactance of a circuit to zero.

$$2 \pi f L - \frac{1}{2 \pi f C} = 0$$

where L is the inductance, C is the capacitance, and f the frequency. In any circuit a frequency may be found at which the reactance is zero. This is the frequency at resonance and is the frequency at which the electron tube oscillator oscillates.

The filament is lighted by a small battery and the plate is charged positively by another battery. Some provision has to be made to vary the charge on the grid. This is accomplished by coupling the plate circuit to the grid circuit electrostatically (by a condenser), or electromagnetically (by an inductance), or by direct connection through a resistance. In the Hartley circuit the grid circuit contains several turns of wire that are connected inductively with several turns of wire in the plate circuit. These same turns are used by the secondary or independent circuit that oscillates, the frequency of which at resonance determines the frequency of the oscillator. The coupling of plate and grid circuits is called feed-back.

If an electric current is passed through a solution anions give up their charge to the anode and cations to the cathode. It is necessary to pass 96,500 (or 96,496) coulombs of electricity (one faraday) in order to deposit 1 gram equivalent of ions on an electrode. If the ions remain on the electrodes, as in electroplating, a gram equivalent of the electrolyte is removed from the solution by the passage of 96,500 coulombs, since a gram equivalent of anions is deposited on the anode and a gram equivalent of cations on the cathode. In any cross-section of the solution x gram equivalents of anions are moved in one direction and 1-x gram equivalents of cations are moved in the opposite direction. Let us suppose that the cations move twice as fast as the anions. If we imagine a plane half-way between the electrodes, twice as many cations will pass in one direction across this plane as anions in the opposite direction, or $\frac{2}{3}$ gram equivalent of cations moves to the cathode while $\frac{1}{3}$ gram equivalent of anions migrates to the anode. Let us further suppose that around the cathode 1 gram equivalent of cations is removed by the electrode and $\frac{2}{3}$ is gained by migration; there would then be a deficiency of $\frac{1}{3}$ gram equivalent of cations at the cathode. At the same time one-third of the anions are lost from this region by migration; or, in other words, $\frac{1}{3}$ gram equivalent of electrolyte is lost. At the anode $\frac{2}{3}$ gram equivalent of electrolyte is lost. From the change in concentration of the electrolyte at the electrodes may be calculated what is called the transport or transference number of the ion. Since the transference number of each ion is the fraction of the total current carried by that ion the ionic speed may be calculated.

RELATIVE IONIC SPEEDS

	Temperature.	Λ.
H^+	0°	223.9
Li^+	0°	19.3
Na^+	0°	25.6
K^+	0°	42.0
Rb^+	18°	67.6
Cs^+	18°	68.2
$\frac{1}{2}\ Mg^{++}$	0°	25.8
$\frac{1}{2}\ Ca^{++}$	0°	29.4
$\frac{1}{2}\ Sr^{++}$	0°	31.7
NH_4^+	0°	39.2
Zn^{++}	18°	89.0
$Zn\,Cl^+$	18°	30.0
$\frac{1}{2}\ Cu^{++}$	18°	47.16
$\frac{1}{2}\ Pb^{++}$	18°	61.1
$\frac{1}{2}\ Pb^{++}$	0°	41.0
$\frac{1}{2}\ Fe^{++}$	18°	46.0
$\frac{1}{3}\ Fe^{+++}$	18°	43.0
OH^-	18°	174.0
F^-	18°	46.64
Cl^-	0°	40.7
Br^-	0°	41.7
$\frac{1}{2}\ SO_4^{--}$	0°	42.6
NO_3^-	0°	41.2
I^-	0°	43.4
I^-_3	0°	23.8
ClO_2^-	25°	51.0
NO_2^-	25°	75.4
Br^-	18°	65.5
HSe^-	25°	70.5
NO^-	0°	38.0
HCO_3^-	25°	46.2
AlO_2^-	16°	18.0
$Fe(CN)_6^{----}$	25°	110.2
$Fe(CN)_6^{---}$	25°	93.2
CH_3COO^-	18°	35.0

These values of ionic speeds are relative. The actual speed of ions is slow, as is shown by electrolyzing a solution containing colored anions around the cathode and observing the time necessary for them to reach the anode. The speed of K^+ at infinite dilution (at 18° and 1 volt per cm.) is 0.000669 cm. per sec. The relative speeds of ions may be more conveniently determined by comparing the equivalent conductivities of a series of salts that are completely dissociated. The equivalent conductivity of a salt is proportional to the sum of the ionic speeds of anions and cations $(u + v)$, thus the ratio of the equivalent conductivity of NaCl and KCl is the ratio of the ionic speeds of $Na^+ + Cl^-$ and $K^+ + Cl^-$ $(u + v : u' + v)$. The relative ionic speeds of Na^+ and K^+ are $\Lambda_{NaCl} - \Lambda_{Cl} : \Lambda_{KCl} - \Lambda_{Cl}$. The relative ionic speeds at various temperatures are given in the following table: The temperature coefficient is calculated from the formula, $u_t = u_o (1 + \beta t + \beta' t^2)$, therefore the coefficient for 10° is $1 + 10\beta + 100\beta'$.

The value of β is usually $0.025 - 0.03$ and of β' less than 0.0001 except for H^+ and OH^-, in which case the values are much lower.

THE LAW OF MASS ACTION

According to the law of mass action as formulated by Wilhelmy, the rate of a chemical reaction depends on the concentration of the reacting substance, or the concentrations of the reacting substances. This law may be used in two ways: First, in the study of the rate at which a chemical change takes place, if this rate is of such a magnitude that measurements can be made; and second, in the study of the equilibrium between two chemical reactions taking place in opposite directions, the equilibrium point being determined by the relative velocities of the two reactions in the two directions, in what is called a reversible reaction.

1. The rate at which a substance is transformed into another chemical form depends on the concentration of the substance. Let 1 represent the original or total concentration, and x represent the concentration of the second substance; it follows that 1-x

represents the concentration of the first substance at any moment during the reaction. The rate of transformation at any moment depends on the concentration of the first substance (1-x) at that moment, and the number expressing this relation is called the reaction constant, *K*. The rate represented by *K* (1-x) decreases as x increases, and at any moment is expressed by the derivative $\frac{dx}{dt}$ which represents an infinitesimal change in x, or *d*x, in an infinitesimal amount of the time, *t*, or *dt*. For example, the rate at which cane-sugar transforms into invert sugar, x, is determined by the concentration (1-x) of the cane-sugar at the moment at which the rate is measured, and is expressed by the derivative $\frac{dx}{dt}$ which indicates that an infinitesimal change *d*x in the concentration of invert sugar, x, takes place in an infinitesimal amount, *dt*, of the time, *t*. The concentration of the cane-sugar at any moment is denoted by (1-x), in which 1 stands for the concentration at the start. The equation representing the rate of the reaction is $\frac{dx}{dt} = K\ (1\text{-}x)$. In this case *K* is the constant of the reaction of inversion of cane-sugar.

2. In certain cases in which the reactions are so rapid that the rates have not been studied, the reactions are reversible and when equilibrium has been established the rate of transformation of the first substance into the second is equal to the rate of transformation of the second substance into the first. For instance, in the dissociation of an acid such as acetic acid, there is also a process of association of the ions to form the acid expressed by the equation

$$[\mathrm{H^+}] + [\mathrm{OAc^-}] \rightleftarrows [\mathrm{H\ OAc}]$$

At equilibrium

$$[\mathrm{H^+}] \times [\mathrm{OAc^-}] = K\,[\mathrm{H\ OAc}]$$

In this case *K*, the reaction constant, is called the dissociation constant.

$$\frac{[\mathrm{H^+}] \times [\mathrm{OAc^-}]}{[\mathrm{H\ OAc}]} = K$$

This same relation was expressed by Ostwald, to show the effect of dilution, by the equation

$$\frac{a^2}{V(1-a)} = K$$

where a represents the degree of dissociation of the H OAc, $\frac{a}{V}$, the concentrations of $[H^+]$ and $[OAc^-]$ (the two being equal), and $\frac{(1-a)}{V}$ the concentration of the undissociated portion. The equation above is given under Electric Conductivity in terms of conductance ratio.

Reaction constants may also be calculated from the table of free energies. The method is as follows:

In a chemical reaction part of the energy transferred may be made to do work and is called the change in free energy, δF. The rest of the energy transferred is transformed into heat and is denoted by q. In any chemical reaction if the change in free energy, δF, has a large positive value (*i. e.*, energy is absorbed during the reaction) the reaction would not occur to any measurable extent, but if it has a large negative value (*i. e.*, energy is evolved) the reaction may run almost completely. If the numerical value of the change in free energy is small, either positive or negative, the reaction may usually be made to proceed in either direction by a choice of concentrations.

If we divide δF, the difference in free energy, by -1364.9, we find the corresponding logarithm of the equilibrium constant, assuming the temperature is always 25°.

The following example shows the use of the table below,

$$I^- + NO_2^- + 2H^+ = \tfrac{1}{2}\, I_2\,(s) + NO\,(g) + H_2O\,(l);$$
$$-12361 - 8500 + 0 = 0 + 20850 - 56560$$
$$\delta F = -14849$$

in which s denotes solid; g, gaseous, and l, liquid.

In the following table, taken from Lewis and Randall, the free energy of formation of various substances in a standard state at 25° is given. In order to use these data the algebraic sum of the free energies of the right-hand and left-hand parts of the equation are made and the total free energy of the reaction then determined.

TABLE OF STANDARD FREE ENERGIES OF FORMATION AT 25°

Equation.	δ F.
$\frac{1}{2} H_2 = H^+ + e$	0
$Li = Li^+ + e$	−68248
$Na = Na^+ + e$	−62588
$Na + \frac{1}{2} Cl_2 (g) = NaCl (s)$	−91792
$K = K^+ + e$	−67431
$K^+ + ClO_3^- = KClO_3 (s)$	−69250
$Rb = Rb^+ + e$	−67473
$Cu = Cu^{++} + 2e$	−15912
$Ag = Ag^+ + e$	18448
$Ag + \frac{1}{2} Cl_2 (g) = AgCl (s)$	−26187
$Ag + \frac{1}{2} O_2 = Ag_2O (s)$	−2395
$2 Hg = Hg_2^{++} + 2e$	36854
$Hg + \frac{1}{2} Cl_2 (g) = HgCl (s)$	−25137
$Hg (l) + \frac{1}{2} O_2 = HgO (s)$	−13808
$Tl = Tl^+ + e$	−7760
$Tl + \frac{1}{2} Cl_2 (g) = TlCl (s)$	−44164
$2Tl (s) + \frac{1}{2} O_2 = Tl_2O (s)$	−32410
$Tl + \frac{1}{2} O_2 + \frac{1}{2} H_2 = TlOH (s)$	−45400
$Sn = Sn^{++} + 2e$	−6276
$Pb = Pb^{++} + 2e$	−5630
$Pb + Cl_2 (g) = Pb Cl_2$	−74990
$Pb + \frac{1}{2} O_2 = PbO (s)$	−41000
$Ca (s) + H = CaH_2 (s)$	−34780
$Zn = Zn^{++} + 2e$	−34984
$Cd = Cd^{++} + 2e$	−18348
$\frac{1}{2} H_2 (g) = H (g)$	37730
$O_2 (g)$	0
$3/2 O_2 = O_3$	32400
$H_2 + \frac{1}{2} O_2 = H_2O (g)$	−54507
$H_2 + \frac{1}{2} O_2 = H_2O (l)$	−56560
$H_2 + \frac{1}{2} O_2 = H_2O (s)$	−56418
$\frac{1}{2} O_2 + \frac{1}{2} H_2 + e = OH^-$	−37455
$\frac{1}{2} Cl_2 (g) = Cl (g)$	32400
$Cl_2 (g)$	0
$Cl_2 (g, a = 1) = Cl_2 (g, p = 1)$	−6
$Cl_2 (g) = Cl_2 (l)$	1146
$Cl_2(g) = Cl_2 (aq)$	1650
$Cl_2(g) = Cl_2(in\ CCl_4)$	1030
$\frac{1}{2} H_2 + \frac{1}{2} Cl_2(g) = HCl (g)$	−22692
$\frac{1}{2} Br_2(l) = Br (g)$	18250
$Br_2(l) = Br_2(g)$	755
$Br_2(l)$	0

Equation.	δ F.
$Br_2(l) = Br_2(s)$	314
$Br_2(l) = Br_2(aq)$	977
$Br_2(l) = Br_2(\text{in } CBr_4)$	389
$\frac{1}{2} H_2 + \frac{1}{2} Br_2(l) = HBr\ (g)$	−12540
$Fe = Fe^{++} + 2e$	−20350
$Fe = Fe^{+++} + 3e$	−3120
$\frac{1}{2} N_2 + 2H_2 = NH_4^+$	−18930
$H_2 + O_2 = H_2O_2(g)$	−24730
$H_2(g)$	0
$H_2 + O_2 = H_2O_2\ (l)$	−28230
$H_2 + O_2 = H_2O_2\ (s)$	−27980
$H_2 + O_2 = H_2O_2\ (aq)$	−31470
$\frac{1}{2} H_2 + O_2 + e = HO_2^-$	−15610
$\frac{1}{2} H_2 + \frac{1}{2} Cl_2(g) = HCl\ (aq)$	−31367
$\frac{1}{2} Cl_2(g) + e = Cl^-$	−31367
$\frac{1}{2} (H_2 + Cl_2 + O_2) = HClO\ (aq)$	−19018
$\frac{1}{2} (Cl_2 + O_2) + e = ClO^-$	−6500
$\frac{1}{2} (Cl_2 + H_2 + 3O_2) = HClO_3\ (aq)$	−250
$\frac{1}{2} (H_2 + Cl_2 + 3O_2) + e = ClO_3^-$	−250
$\frac{1}{2} H_2 + Br_2(l) = HBr\ (aq)$	−24595
$\frac{1}{2} Br_2(l) + e = Br^-$	−24595
$3/2\ Br_2(l) + e = Br_3^-$	−25230
$\frac{1}{2} [H_2 + Br_2(l) + O_2] = HBrO\ (aq)$	−19680
$\frac{1}{2} Br_2(l) + 3/2\ O_2 + \frac{1}{2}H_2 = HBrO_3\ (aq)$	2300
$\frac{1}{2} Br_2(l) + 3/2\ O_2 + e = BrO_3^-$	2300
$\frac{1}{2} I_2(s) = I\ (g)$	15470
$I_2(s) = I_2(g)$	4630
$I_2(s) = I_2(l)$	920
$I_2\ (s)$	0
$I_2(s) = I_2\ (aq)$	3926
$\frac{1}{2} [H_2(g) + I_2(s)] = HI\ (g)$	315
$S\ (rh.) = S\ (g)$	30240
$2S\ (rh.) = S_2(g)$	18280
$6S\ (rh.) = S_6\ (g)$	11900
$8S\ (rh.) = S_8(g)$	10000
$S\ (rh.) = S\lambda\ (l)$	94
$S\ (rh.) = S\lambda, \mu\ (l)$	93
$S\ (rh.) = S\ (monocl.)$	18
$S\ (rhomb.)$	0
$H_2 + S\ (rh.) = H_2S\ (g)$	−7840
$H_2 + S\ (rh.) = H_2S\ (aq)$	−6490
$\frac{1}{2} H_2 + S\ (rh.) + e = HS^-$	2980
$N_2(g)$	0
$\frac{1}{2} N_2 + 3/2\ H_2 = NH_3(g)$	−3910
$\frac{1}{2} N_2 + 3/2\ H_2 = NH_3(l)$	−2620
$\frac{1}{2} N_2 + 3/2\ H_2 = NH_3\ (aq)$	−6300
$\frac{1}{2} N_2 + 5/2\ H_2 + \frac{1}{2} O_2 = NH_4OH\ (aq)$	−62860
$\frac{1}{2} N_2 + 2H_2 = NH_4^+ + e$	−18930
$\frac{1}{2} I_2(s) + H_2 = HI\ (aq)$	−12361
$\frac{1}{2} I_2(s) + e = I^-$	−12361
$3/2\ I_2(s) + e = I_3^-$	−12315

Equation.	δ F.
$\frac{1}{2}[H_2 + I_2(s) + O_2] = HIO\ (aq)$	−23170
$\frac{1}{2} I_2(s) + 3/2\ O_2 + e = IO_3^-$	−31580
$\frac{1}{2}[H_2 + I_2(s) + 3O_2] = HIO_3\ (aq)$	−31580
$S\ (rhomb.) + 2e = S^{--}$	23450
$S\ (rh.) + O_2 = SO_2(g)$	−69660
$S\ (rh.) + O_2 = SO_2\ (aq)$	−69770
$S + H_2 + 3/2\ O_2 = H_2SO_3$	−126330
$S + \frac{1}{2} H_2 + e + 3/2\ O_2 = HSO_3^-$	−123920
$S + 2e + 3/2\ O_2 = SO_3^{--}$	−116680
$S + O_2 + Cl_2 = SO_2Cl_2(g)$	−71560
$S\ (rh.) + 2/3\ O_2 = SO_3(g)$	−85890
$H_2 + S + 2\ O_2 = H_2SO_4$	−176500
$2e + S + 2\ O_2 = SO_4^{--}$	−176500
$\frac{1}{2} N_2 + O_2 = NO_2(g)$	11920
$N_2 + 2\ O_2 = N_2O_4(g)$	22640
$\frac{1}{2} H_2 + \frac{1}{2} N_2 + O_2 = HNO_2(aq)$	−13070
$\frac{1}{2} N_2 + O_2 + e = NO_2^-$	−8500
$\frac{1}{2}(H_2 + N_2 + 3\ O_2) = HNO_3(g)$	−18210
$\frac{1}{2}(H_2 + N_2 + 3\ O_2) = HNO_3(aq)$	−26500
$\frac{1}{2} N_2 + \frac{1}{2} O_2 = NO\ (g)$	20850
$\frac{1}{2}(N_2 + O_2 + Cl_2) = NOCl\ (g)$	16010
$C\ (graph) = C\ (diamond)$	390
$C\ (graph)$	0
$C\ (graph) + 2\ H_2 = CH_4(g)$	−12800
$6\ C\ (graph) + 3\ H_2 = C_6H_6(l)$	27100
$C\ (graph) + \frac{1}{2} O_2 = CO\ (g)$	−32510
$C + \frac{1}{2} O_2 + Cl_2 = COCl_2$	−48770
$C + S\ (rh.) + \frac{1}{2} O_2 = COS\ (g)$	−39600
$C\ (graph) + O_2 = CO_2(g)$	−94260
$C\ (graph) + H_2 + 3/2\ O_2 = H_2CO_3(aq)$	−148810
$C + \frac{1}{2} H_2 + 3/2\ O_2 + e = HCO_3^-$	−140000
$C + O_2 + H_2 = HCOOH\ (l)$	−84040
$C + 3/2\ O_2 + 2e = CO_3^{--}$	−125760
$\frac{1}{2} N_2 + 3/2\ O_2 + e = NO_3^-$	−26500
$C\ (graph) + O_2 + H_2 = HCOOH\ (aq)$	−87920
$2\ C + 3\ H_2 + \frac{1}{2} O_2 = C_2H_5OH\ (l)$	−45100
$C + \frac{1}{2} O_2 + N_2 + 2\ H_2 = CO(NH_2)_2(s)$	−47280
$C + \frac{1}{2} O_2 + N_2 + 2\ H_2 = CO(NH_2)_2(aq)$	−48840
$C + \frac{1}{2}(N_2 + H_2) = HCN\ (g)$	28910
$C + \frac{1}{2}(N_2 + H_2) = HCN\ (l)$	28870
$C + \frac{1}{2}(N_2 + H_2) = HCN\ (aq)$	27520
$C + \frac{1}{2} N_2 + e = CN^-$	39370
$C + \frac{1}{2}(H_2 + N_2 + O_2) = HCNO\ (aq)$	−29100
$C + e + \frac{1}{2}(N_2 + O_2) = CNO^-$	−23750
$C + \frac{1}{2} N_2 + \frac{1}{2} I_2(s) = CNI\ (s)$	42790
$2\ C + N_2 = C_2N_2$	92000

SOLUBILITY PRODUCT

Ionization must be considered in studying the solubility of electrolytes. If we pass hydrochloric acid gas into a saturated solution of NaCl the salt will partially crystallize out. In a saturated solution of NaCl the product of the concentration of Na^+ and Cl^- is a constant, and when we introduce more Cl^- by the addition of HCl, salt crystallizes out until the product resumes its original value. The product of the ions in the saturated solution is called the *solubility product,* and if this product is exceeded the solution is supersaturated. Crystallization may not take place, however, unless nuclei to start the crystallization are present. In the ocean the solubility product of Ca^{++} and CO_3^{--} is exceeded and the solution is, therefore, supersaturated in regard to calcium carbonate. Calcium carbonate, however, does not precipitate throughout the ocean because the proper nuclei for crystallization are not present. Calcium carbonate crystallizes in different forms, the most common of which are calcite and aragonite. Aragonite is 10 per cent. more soluble than calcite, but ocean water is supersaturated even to aragonite, and if it is shaken with either aragonite or calcite crystals at any temperature such as actually occurs in the ocean, there is a growth of these crystals and a decrease of the Ca^{++} and CO_3^{--} in solution.

HYDROLYSIS

In case one of the radicals of an electrolyte is weak and the other strong, hydrolysis may occur. This has been usually represented as follows: $KHCO_3$ hydrolyzes and forms KOH and H_2CO_3. Since the former dissociates more than the latter, a greater number of OH ions are present in the solution than H ions and the reaction is alkaline. This may be pictured differently, since, according to Debye, no undissociated KOH molecules are ever formed:

$$KHCO_3 \rightarrow K^+ + HCO_3^-$$

$$H_2O + HCO_3^- \rightleftarrows OH^- + H_2CO_3$$

AMPHOLYTES

Some substances may dissociate H^+ or OH^- and are, therefore, called amphoteric electrolytes or ampholytes. Some of them may be neutral; in others the acidic or basic character may predominate, depending upon the dissociation constants of the acid and basic portions of the molecule.

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CHAPTER V

HYDROGEN IONS

The activity, *a*, of a metallic ion in solution may be studied by the electromotive force produced when this solution is used in a galvanic cell in which the metal forms the electrodes. If the activity of the ion around one electrode is different from that around the other electrode, an electromotive force is produced because of the electrolytic solution-tension of the metal. This may be explained as follows:

If a metal plate is placed in a polar solvent, such as water, the metal tends to go into solution. As each atom leaves the metal electrode it becomes oxidized and is now more positive than the metal. In fact, each atom leaves one or more electrons in excess in the metal, giving the metal a negative charge and the atom receiving a positive charge. On the other hand, when there is an excess of charged atoms or ions in solution they plate out on the metal, and in doing so are reduced and lose their positive charge to the metal which then acquires a more positive charge than it previously possessed. At equilibrium the charge on the metal is just sufficient to maintain the activity of ions at a constant level because of the electrostatic attraction for these ions. When placed in a normal solution of metallic ions each metal has its own characteristic difference of potential when compared with a normal hydrogen electrode as shown in the following table (which includes also some anions). The sign of the potential indicates the charge on the solution in contact with the metal at 25° (Lewis and Randall) which is opposite to the method of expression used by Abegg, Auerbach, and Luther, who indicate the charge on the metal:

Element.	Ion.	Electrolytic solution-tension in volts.
Li,	Li^+	2.9578
Rb,	Rb^+	2.9242
K,	K^+	2.9224
Na,	Na^+	2.7125
Zn,	Zn^{++}	0.7581
Fe,	Fe^{++}	0.441
Cd,	Cd^{++}	0.3976
Tl,	Tl^+	0.3363
Sn,	Sn^{++}	0.136
Pb,	Pb^{++}	0.122
Fe,	Fe^{+++}	0.045
Pt, H_2,	H^+	0.000
Cu,	Cu^{++}	−0.3448
Hg,	Hg_2^{++}	−0.7986
Ag,	Ag^+	−0.7995
Pt, OH^-,	O_2	−0.3976
Pt, I^-,	$I_2(s)$	−0.5359
Pt, Br^-,	$Br_2(l)$	−1.0659
Pt, Cl^-,	$Cl_2(g)$	−1.3594

Hydrogen has certain metallic properties and is, therefore, listed in the table as a metal. In the practical study of these metals many of them are dissolved in other metals to form dilute amalgams or alloys, in which case the electromotive force calculated from the solution-tension of the dissolved metal is related to its activity in the amalgam. Very reactive metals, such as sodium and potassium, are dissolved in mercury. Hydrogen is alloyed with platinum, palladium, or iridium. Hydrogen is considered monatomic in the metal (Bodenstein). The electromotive force of hydrogen is that of the alloy in equilibrium with hydrogen gas at the pressure of one atmosphere.

Since osmotic pressure, P, is inversely proportional to volume, V, the equation for work becomes:

$$w = RT \log_e \frac{a_1}{a_2}, \qquad (1)$$

in which a_1 and a_2 are the activities of the hydrogen ions in the two hydrogen electrodes connected to form an electrolytic cell.

This work is the work the hydrogen ions in a cell composed of 2 hydrogen electrodes can do on a voltmeter. When these electrodes are connected so as to form a short-circuited cell the solution with greater concentration of hydrogen ions will deposit some of them on the electrode, and positive electricity, after flowing through the wire to the other electrode, will be given to new hydrogen ions entering the more dilute solution. In this way the osmotic pressure of the hydrogen ions is converted into electromotive force, E. In order to make this equation (1) express electromotive force R is expressed in joules per degree and RT must be divided by 96,500 (or 96,494), since the passage of this number of coulombs of electricity (1 faraday) is required in order to deposit 1 gram equivalent of ions on an electrode. Logê may be converted into the common logarithm (to base 10) by multiplying by 2.3026. The equation then becomes:

$$E = \frac{8.316\ T\ 2.3026}{96500} \log \frac{a_1}{a_2}$$

$$= 0.000198427\ T \log \frac{a_1}{a_2} \qquad (2)$$

If a_1 is a gram equivalent solution of hydrogen ions,

$$\log \frac{a_1}{a_2} = \log \frac{1}{a_2}$$

$$= -\log a_2$$

and

$$-\log a_2 = \frac{E}{0.0001984\ T} \qquad (3)$$

from which formula it is possible to calculate the activity (a_2) of hydrogen ions in a hydrogen electrode connected with another hydrogen electrode containing a normal solution of hydrogen ions (a_1). It is more convenient, however, to use a calomel electrode in place of the normal hydrogen electrode, in which case a correction (E_o) of 0.3351 volts for the 0.1 N KCl calomel electrode is applied and the formula becomes

$$-\log a_2 = \frac{E - E_o}{.0001984\ T} \qquad (4)$$

It is often convenient to leave the result in the value of the logarithm of the reciprocal of the hydrogen ion activity ($-\log a_2$), designated by pH. If the temperature is 22° T is 295 and the calomel electrode 0.1 N,

$$p\text{H} = \frac{E - 0.3351}{0.058523} \qquad (5)$$

By means of the hydrogen electrode and formula (4) the hydrogen ion activity of pure water due to the dissociation of the water molecule into hydrogen and hydroxyl ions is estimated as 0.0000001 N at about 23°. This value is about the same as that determined from electric conductivity data—*i. e.*, the agreement is close considering the possibility of error in measurement of electric conductivity. The measurement of the hydrogen ion activity is more accurate than measurement of conductivity in dilute solutions.

At higher activities of hydrogen ions in a solution of HCl the activity, as determined from hydrogen electrode, is not the same as the conductance ratio. If conductance ratio and activity are taken to be concentration the data obtained by the latter method indicate that as the concentration increases the dissociation decreases, whereas from the electromotive force we should have to conclude that at higher concentration of HCl the dissociation is greater than 100 per cent. For this reason it is assumed that neither conductance ratio nor activity are measures of the concentration of the hydrogen ions except at infinite dilution. Debye assumes that strong acids are completely dissociated in aqueous solutions of any concentration. On the basis of Debye's theory, A. A. Noyes calculates the concentration from the activity by means of the following formula:

$$\log_e a = \frac{7.77 \times 10^{15}\, \text{V}^2 \sqrt{\Sigma\,(c\, \text{V}^2)}}{8.32 \times 10^7\, (k\ T)^{1.5}}$$

where c is concentration in mols per cubic centimeter, V is valence, k is the dielectric constant of the solvent, and T the absolute temperature.

Except in the gastric juice the concentration of hydrogen ions in living organisms is so low that the activity equals the concentration, and hence we believe that the use of the terms H^+ concentration and pH do not cause any appreciable error or misunderstanding.

OXIDATION-REDUCTION

When an electron passes from one atom to another the atom losing the electron is said to be oxidized and the atom gaining it to be reduced. The atom losing the electron, if free, becomes a positive ion and can combine with a negative ion. Thus, the hydrogen atom is oxidized by the removal of its electron and becomes a hydrogen ion with a valence of one, which is its maximum valence. The cuprous ion, Cu^+, becomes oxidized by the loss of an electron, becoming the cupric ion, Cu^{++}, its valence changing from one to two by the oxidation. The ferrous ion, Fe^{++}, oxidized by the loss of an electron, becomes the ferric ion, Fe^{+++}, its valence changing from two to three. Oxygen in oxygen gas by its affinity for electrons has an oxidizing action, and hydrogen gas, by giving up electrons, has a reducing action. If an electric current is passed through water, OH^- and H^+ carry the current between the electrodes and the H^+ is reduced to gaseous hydrogen at the negative electrode and the OH^- is oxidized to gaseous oxygen and water at the positive electrode. The electric character of oxidation and reduction may be shown in the following manner: Connect the two leads of a galvanometer to platinum wires and insert the free ends of the platinum wires into the two openings of a U-tube filled with salt water. To one arm of the U-tube add an oxidizing agent and to the other arm a reducing agent. The galvanometer will indicate that the oxidizing arm of the U-tube is electro-positive and the reducing arm electro-negative.

The relation between oxidation-reduction and hydrogen ion concentration is illustrated by the following example: A certain mixture of ferrocyanide and ferricyanide is inactive toward indophenol in neutral or alkaline solutions, but at a hydrogen ion concentration greater than 0.0001 N the ferrous ion is oxidized by the indophenol.

In the interior of a solution when one substance is oxidized another is reduced. Hydrogen ions are oxidative, but they can only accomplish oxidation of another substance with simultaneous decrease in hydrogen ion concentration, for example, according to the equation:

$$2I + 2(NO_2^-) + 4H^+ \rightarrow I_2 + 2(NO) + 2H_2O$$

If the hydrogen ions remain constant some other substance must be reduced when a third is oxidized. If, however, the oxidation-reduction potential is given in volts, increase of hydrogen ion concentration of a solution makes the electrode inserted into it more electropositive, and electro positiveness is interpreted as oxidative power.

HYDROGEN ELECTRODES

The hydrogen electrode must be contained in a special vessel which will retain the hydrogen gas. Hydrogen electrodes are of such very numerous forms that space does not allow us to discuss them all. Only a few will be selected. In Type I (Fig. 5), a gold plate, attached to a platinum wire fused through the wall of the vessel, is plated with iridium by using it as cathode for a few seconds in a concentrated solution of iridium chloride.

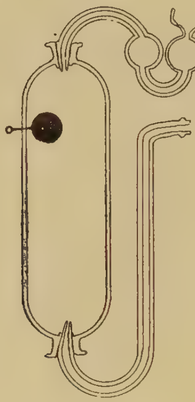


Fig. 5.—Hydrogen electrode vessel for ordinary work. Hydrogen is admitted through the tube at the bottom and bubbles out of the U-tube at the top. The U-tube contains a drop of water which acts as a trap. The metal disk should be entirely immersed in the solution when the reading is made. The ground joint at the bottom serves as a connection with the calomel electrode by immersion in a saturated solution of KCl. (From Journal of Biological Chemistry.)

It is then washed in water and preferably kept wet with distilled water when not in use. The electrode is entirely immersed in the unknown solution, which partially fills the vessel. Passing to the bottom of the vessel is a tube admitting hydrogen gas, which bubbles out through a hole in the stopper. At the extreme bottom is an ungreased cock or ground joint which will conduct the electric current through the moisture wetting the moving surface of the stop-cock or ground joint when it is immersed in a bath of saturated KCl solution connected to the other electrode. If no volatile acids are present pure hydrogen is constantly bubbled through the solution. In case the solution contains volatile acids, such as CO_2, the bubbling of the hydrogen drives off the CO_2 and changes the hydrogen ion concentration; hence the electrode must be filled once with hydrogen and then closed.

The Clark electrode (Fig. 6) has been used by Clark with great success and is figured as the second type. This vessel is entirely filled with a solution and then the hydrogen is run in, displacing some of the solution. It is then closed and rocked by a mechanical rocker to bring the hydrogen into equilibrium with the solution in CO_2 tension. In the process of rocking all of the oxygen finally reaches the iridium surface, where, by the catalytic action of the iridium, it combines with hydrogen to form water. During the time that this process is taking place the hydrogen pressure in the iridium is less than that of an atmosphere, and the readings are incorrect. Therefore it has to be rocked for a considerable period of time in order that a constant potential

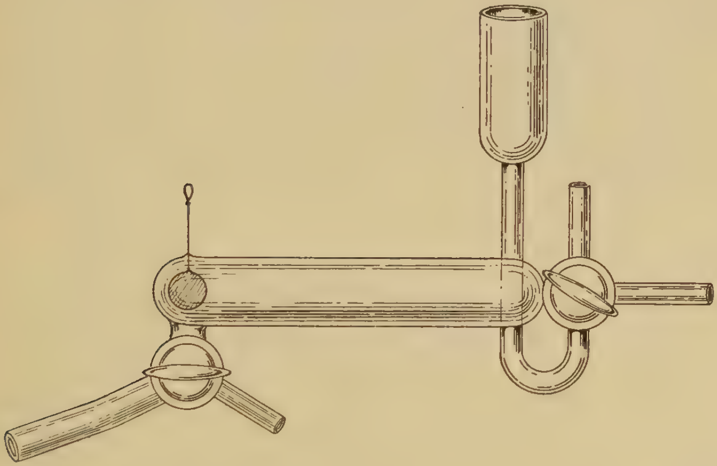


Fig. 6.—Clark hydrogen electrode vessel. The three-way cock below the metal disk serves for draining the vessel and connecting to it the calomel electrode. It is automatically rocked by means of a motor.

be reached. The electromotive force is determined only while the electrode is immersed in the solution, as otherwise it will drain off to molecular thickness and the concentration of hydrogen ions will not be the same as in the main body of the solution. Some solutions that contain very high concentrations of bicarbonates are changed by shaking with even a small amount of hydrogen as the hydrogen takes away an appreciable amount of the CO_2. These can be determined in the Clark electrode by allowing new portions of the unknown solution to enter the electrode while a portion of the old is drained out through the bottom. This brings in new quantities of oxygen and the rocking has to continue for some time.

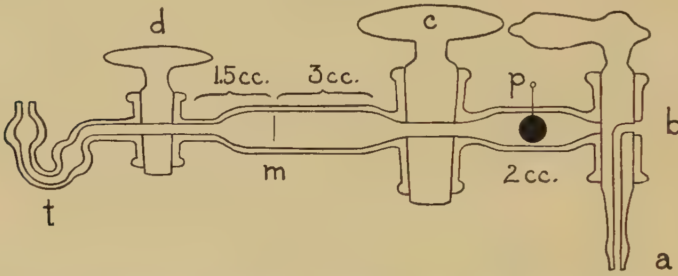


Fig. 7.—Hydrogen electrode vessel for use with blood-plasma. The vessel is filled with hydrogen gas. Then the plasma is admitted through *a*, driving the air out at *d*, and then forced in to the point *m*. All cocks are closed and it is shaken, and by opening *c* and tapping hydrogen passes into *b*. Connection with the calomel electrode is made by immersing the ungreased cocks *b* and *c* in saturated KCl solution. (From Journal of Biological Chemistry.)

For anything like blood-plasma several changes would be necessary and a large quantity of blood-plasma would have to be used. For this purpose the third type of electrode (Fig. 7), in which only a little solution is needed, is recommended. The electrode vessel consists of two chambers connected by a large stop-cock of about 4 mm. bore. The electrode is completely filled with hydrogen and then the small chamber and half of the large chamber are filled with the unknown—*i. e.*, blood-plasma or other solution containing CO_2. The stop-cocks are closed and the vessel is shaken, bringing the hydrogen into equilibrium with the solution in the large chamber. During this process the solution has somewhat changed, so the middle stop-cock is opened and, by tapping the electrode, bubbles of hydrogen are made to pass into the small chamber, being washed as they pass by the stream of the solution flowing back into the large chamber. In this way they reach the CO_2 tension of the original solution.

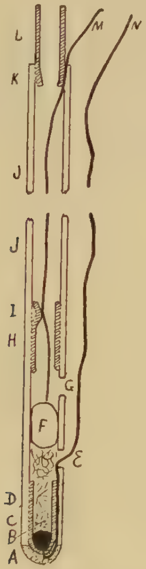


Fig. 8.—Combined calomel and hydrogen electrode vessel that may be swallowed for the direct determination of hydrogen ions in the stomach. (From American Journal of Physiology.)

This type of electrode is used for very viscid solutions like blood-plasma which will maintain a thick film for a considerable time on the electrode surface. Only a small amount of the solution is left in the small chamber, the remainder of the space being occupied by hydrogen gas. The stop-cock is closed and the electrode vessel shaken again. The two stop-cocks closing the ends of the small chamber are not greased, but are lubricated with a saturated solution of KCl, which conducts the current. They are dipped in a KCl bath. After shaking the electrode vessel, enough solution clings to the walls for a few minutes during which the reading can be taken. The second reading, however, should be preceded by renewed shaking. Owing to the small size of the chamber very little oxygen will be in it, and only a short time is required to attain the final equilibrium. In preparing a blood sample a tube is prepared with enough oxalate in it to make 0.1 per cent. oxalate in the blood. This is then dried as a film over the whole inner surface. A hypodermic needle connected to the tube is inserted into the vein and the blood run in so as not to drop through the air. It is best to fill the tube completely and

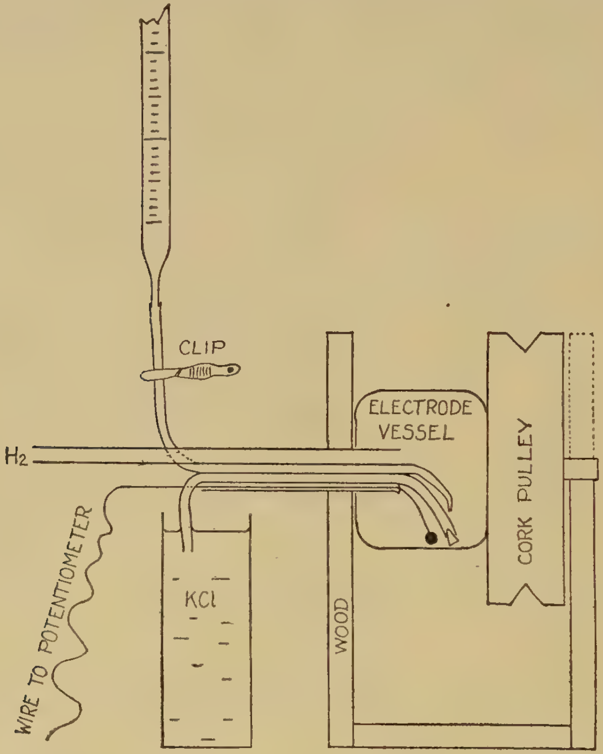


Fig. 9.—Rotating hydrogen electrode vessel for electrometric titration of frothing fluids. (From Journal of Biological Chemistry.)

let the bright red surface-blood overflow. The tube is closed with rubber or melted paraffin and centrifuged to get rid of the corpuscles containing oxyhemoglobin. The plasma is run into the electrode without coming in contact with the air. In Fig. 8 is shown an electrode that may be swallowed, in Fig. 9 is one for the titration of blood-plasma, and in Fig. 10 one for solutions at any desired CO_2 pressure.

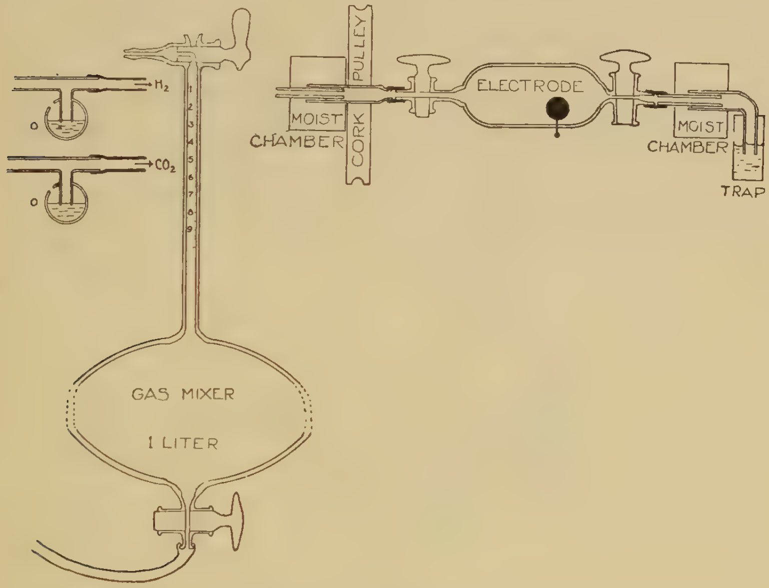


Fig. 10.—Gas mixer and hydrogen electrode vessel for the determination of hydrogen-ion concentration at any desired CO_2 tension. (From Journal of Biological Chemistry.)

It should be noted that besides oxygen other substances affect the electrode. Arsine ($As\ H_3$) and mercury affect it permanently, so that all subsequent readings are worthless. In Fig. 11 is represented a generator for electrolytic hydrogen, free from arsine.

In the practical measurement of hydrogen ion concentration one method is to set up a cell of two hydrogen electrodes, one of them with a known hydrogen ion concentration, and from the electromotive force of the cell calculate the concentration of the unknown. Another method is to substitute a calomel electrode for the hydrogen electrode. As will be seen from the table of electromotive force, mercury in a gram equivalent solution of mercurous ions is positive, the solution being negative. If we reduce the concentration of the mercurous ions the positiveness of the mercury will be reduced and, owing to the low solubility of calomel, the potential of this electrode coupled with a normal hydrogen electrode is very small. The potential is still further reduced by adding the chloride solution, the increase in the Cl ions decreasing the solubility of the calomel. The potassium chloride also forms a convenient electric conductor for connection with the hydrogen electrode. When coupled with the normal hydrogen electrode a calomel electrode containing 0.1 *N* KCl has a potential of about 0.3351 volts at 25°. This value is not

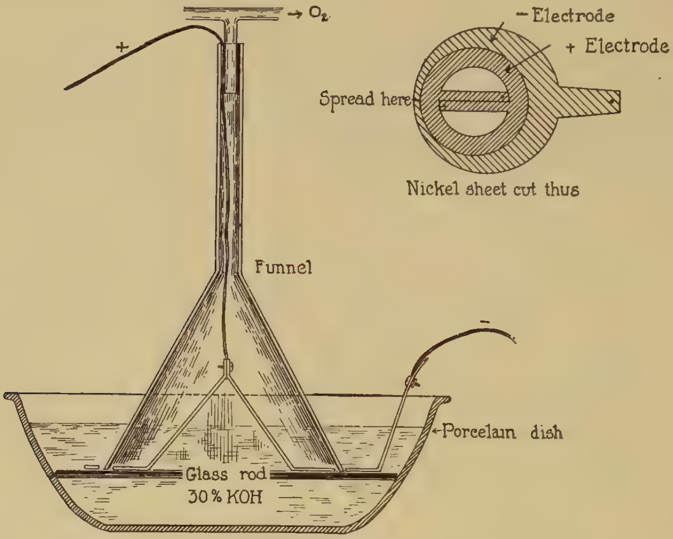


Fig. 11.—Convenient electrolytic hydrogen generator. By means of the T-tube at the top a battery of these generators may be set up connected in series for use with the direct current lighting circuit. In the upper right-hand corner is shown the pattern for cutting out the sheets of nickel for the electrodes.

very much changed by temperature. When the KCl concentration is increased to a normal solution the value is decreased to 0.283. If the KCl is saturated by contact with KCl crystals, the potential is still further reduced and is very much influenced by changes of temperature which cause variations in the concentration of KCl. The electromotive force of this type of cell may be computed from the formula

$$pH = \frac{E - E_0}{0.001984\ T} \qquad (4)$$

The values of the electromotive force for a temperature of 25° are given in the following table based on Lewis and Randall:

ELECTROMOTIVE FORCE IN MILLIVOLTS OF HYDROGEN ELECTRODES AGAINST 0.1 *N*, *N* AND SATURATED CALOMEL ELECTRODES AT 25°. (*N* = 1 mol KCl in 1000 g. H_2O and 0.1 *N* = 0.1 of this.)

*p*H.	0.1 *N*.	*N*.	Sat.
0	335	282	246
1	394	341	305
2	454	400	364
3	512	459	423
4	572	519	482
5	631	578	541
6	690	637	600
7	749	696	659
8	807	755	718
9	867	814	777
10	927	874	837
11	986	933	896

Clark's values for 0.1 *N* and *N* calomel electrodes are nearly 3 millivolts higher, because of using concentration obtained from conductance ratio, whereas here $pH = \log \frac{1}{a}$ where a = activity of H^+. Since a number of assumptions are involved, the reader is referred to the authors quoted. A normal calomel electrode contains one mol KCl in 1000 grams of H_2O, and a 0.1 *N* contains one-tenth this concentration. To be strictly correct the barometric pressure and vapor tension of H_2O should be considered, which involve less than a millivolt correction at 25°.

A saturated KCl calomel electrode has several advantages—

it has a higher conductivity; it is more quickly prepared since the KCl does not have to be weighed, and the concentration of KCl does not change by evaporation nor by immersion in the saturated KCl bath. The electrode should not, however, be subjected to quick changes in temperature, as it requires many hours to come close enough to equilibrium for this type of work. When the calomel and hydrogen electrodes are connected to form a closed circuit an electromotive force is produced at the liquid junction, since the two electrodes contain different electrolytes with different concentrations of anions and cations. The magnitude of the electromotive force depends on the difference in the speeds of the anions and cations. Speeds of diffusion differ considerably because of differences in effective mass. The average kinetic energy of the average molecule in a solution is the same regardless of its mass. Kinetic energy $= \frac{m\,v^2}{2}$, where m represents mass and v, velocity. Since hydrogen is the ion of smallest mass, even when hydrated, it is the swiftest. The algebraic sum of the ionic speeds of H^+ and K^+ represents the value of the electromotive force at the liquid junction. Although these liquid junctions are very troublesome in calculations, still they can be calculated. Planck made a formula for electromotive force assuming a knife edge separation of uni-univalent electrolyte solutions.

$$E = \frac{R\,T}{\mathbf{F}} \log_e \frac{u_1 + v_2}{u_2 + v_1}$$

where E is the electromotive force at the liquid junction, v_1 and u_1 the speeds of cation and anion of one electrolyte, and v_2 and u_2 the ionic speeds of the other electrolyte which is in the same concentration. If the concentrations are different the formula is more complicated. Henderson made another one, assuming a region of mixing by convection and diffusion of the two electrolytes:

$$E = \frac{R\,T}{\mathbf{F}} \frac{(u_1 - v_1) - (u_2 - v_2)}{u_1 + v_1 - u_2 + v_2} \log_e \frac{u_1 + v_1}{u_2 + v_2}$$

The observed electromotive force is somewhere between these limits designated by these formulas. G. N. Lewis and Sargent used an empiric formula that was found to give values closer to the observed values.

Since the magnitude of the electromotive force depends on the difference in the speeds of the anions and cations, its value will be great only when the electrolyte consists of a large percentage of some substance like HCl in which the hydrogen ions travel much more rapidly than the other ions. Therefore it is not possible to measure the hydrogen ion concentration of concentrated solutions of HCl without using a formula for this electromotive force. When studying solutions near the neutral point, however, the formula may be dispensed with if the junction is so constituted that the majority of the anions and cations travel at the same speed. Since the very few hydrogen and hydroxyl ions will influence the electromotive force only in proportion to their concentrations, it is necessary to increase the concentration of other ions as much as possible. As potassium chloride is unique in having the speed of the anions and cations about equal, a saturated solution of potassium chloride is used at the junction.

The calomel electrode vessel must be painted black to prevent light from decomposing the calomel into Hg and mercuric chloride. The latter is more soluble than mercurous chloride and introduces a new species of Hg ions.

The measurement of electromotive force is made most simply by the use of a quadrant electrometer. Since this electrometer does not require an appreciable amount of current it does not change the cell by short-circuiting it, as would a voltmeter of the ordinary type. The delicacy of this instrument, together with the necessity of shielding it from static charges, however, has made it rather unpopular.

The other method that is practicable is that of the potentiometer. The potentiometer consists of a wire through which an electric current is flowing. Along this wire there is a drop in potential, so that by determining the fall of potential it is possible to pick out two points of any difference in potential. A uniform drop is secured by having the wire of uniform thickness and therefore of uniform resistance. This wire is made 1.0183 meters long. Through it a current passes from an ordinary lead storage cell. A rheostat is placed in the circuit so that the amount of current and difference in the potential of the two ends of the potentiometer wire may be varied. The two ends of the wire are connected through a key with a Weston standard cell of an electromotive force of 1.0183 volts. By putting a galvanometer in the circuit with the standard cell it may be determined whether a current is flowing or not. When the rheostat is adjusted so that the two ends of the potentiometer wire have a difference in potential of 1.0183 volts and the poles of the standard cell are connected in the same direction as the poles of the potentiometer wire, no current will flow through the galvanometer. This condition is reached after each millimeter on the potentiometer wire corresponds to a difference in potential of one millivolt. When a determination of the electromotive force of the cell consisting of hydrogen and calomel electrodes is to be made, the

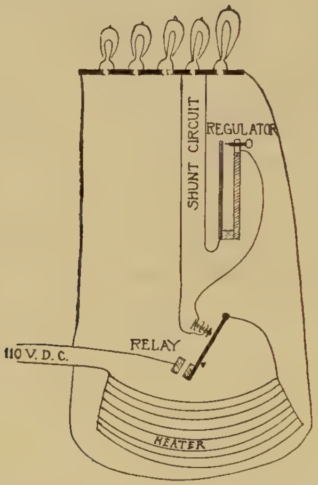


Fig. 12.—Electric heater, relay, and bimetallic (invar-brass) regulator used for obtaining constant temperature. (From Journal of Biological Chemistry.)

cell is turned so that the calomel electrode is marked + and the hydrogen – and set in place of the Weston cell. The contact from the positive pole is then made to slide along the potentiometer wire until the galvanometer shows no deflection. The millimeters measured from the negative end to the sliding contact now gives the millivolts of electromotive force of the hydrogen-calomel cell. By use of the formula previously explained (4) after subtracting the calomel electrode constant (E_o) from the total, the hydrogen ion concentration is obtained.

Owing to the danger of short-circuiting through the water of a water-bath, an oil or air-bath is preferred in maintaining constant temperature. Figure 12 shows an electric regulator and heater for an air-bath or constant temperature room.

BUFFERS

Buffers, are weak acids or bases, the latter having relations the reciprocal of those of the former. They behave in dissociation similarly to indicators—*i. e.*, when dissociation reaches about 50 per cent. a slight change in the *p*H causes a marked change in the degree of ionization. This is the region of maximum buffer action. The concentration of the buffer must be high and of an indicator, low. To illustrate: If a buffer acid is in double normal solution and is 50 per cent. dissociated, the hydrogen ions given out by the buffer will be a normal solution. These may or may not combine with hydroxyl ions. Assuming that they do not, the most sensitive range of the buffer is $pH = 0$ or a normal solution of hydrogen ions. In order to increase the dissociation of the buffer to 100 per cent. it is necessary to add alkali at least sufficient to neutralize all of the buffer acid—in other words, to add alkali up to double normal. The solution is therefore fairly stable against small additions of alkali. Moreover, in the presence of small amounts of alkali the dissociation of the buffer is increased, whereby hydrogen ions are liberated, but these hydrogen ions combine with the hydroxyl ions of the alkali. Hence compensation occurs over a short range of maximum efficiency of the buffer acid. The point of 50 per cent. dissociation of the buffer acid varies with the dissociation constant just as in the case of the indicators treated in the next section.

In case of small additions of acid the dissociation of the buffer is reduced, and hence hydrogen ions removed, but there is at the same time a gain in hydrogen ions from the acid added, so that the two processes tend to compensate.

Van Slyke has developed a mathematical treatment of buffer

Reciprocals of the Logarithms of Dissociation Constants of Buffers at 25°

—log K_a	Acid.	—log K_a	Acid.
— .92	Trichloracetic	10.22	Carbonic (CO_3^{--})
+1.00	Oxalic	11.00	Chloral hydrate
1.29	Dichloracetic	11.74	Maltose
1.96	Phosphoric ($H_2PO_4^-$)	12.06	Levulose
2.81	Monochloracetic	12.23	Dextrose
2.96	Salicylic	12.23	Lactose
3.01	Tartaric	12.43	Arabinose
3.08	Citric	12.44	Phosphoric (Po_4^{---})
3.40	Malic	12.72	Sucrose
3.65	Hippuric	13.47	Mannite
3.68	Formic	14.15	Glycerol
3.82	Acetoacetic	14.74	Propionitrile
3.85	Lactic		
4.17	Succinic	—log K_b	Base.
4.18	Benzoic	2.80	Piperidine
4.25	Acrylic	2.90	Diethylamine
4.44	Adipic	3.25	Ethylamine
4.49	Gallic	3.27	Dimethylamine
4.7	Betahydroxybutyric	3.39	Methylamine
4.73	Acetic	4.07	Ethylenediamine
4.80	Butyric	4.22	Trimethylamine
4.82	Valerianic	4.34	Allylamine
4.84	Propionic	4.74	Ammonia
4.84	Caproic	4.77	Brucine
4.84	Caprylic	5.58	Quinine
5.80	Uric	6.07	Strychnine
5.80	Salicyl aldehyde	7.00	Atropine
6.00	Tannic	7.00	Pilocarpine
6.05	Phosphoric (HPO_4^{--})	8.64	Pyridine
6.19	Cacodylic	9.30	Aniline
6.52	Carbonic (HCO_3^-)	9.50	o-Toluidine
7.24	Hydrogen sulphide	9.58	Methylaniline
9.24	Boric ($H_2PO_3^-$)	9.62	Dimethylaniline
9.33	Hydrocyanic	9.80	Ethylaniline
9.92	Phenol	13.80	Urea

solutions, the buffer value being $\frac{dB}{d\,p\text{H}}$ or mols of strong base necessary to produce unit change in pH.

Buffer mixtures of wide range of pH may be prepared by

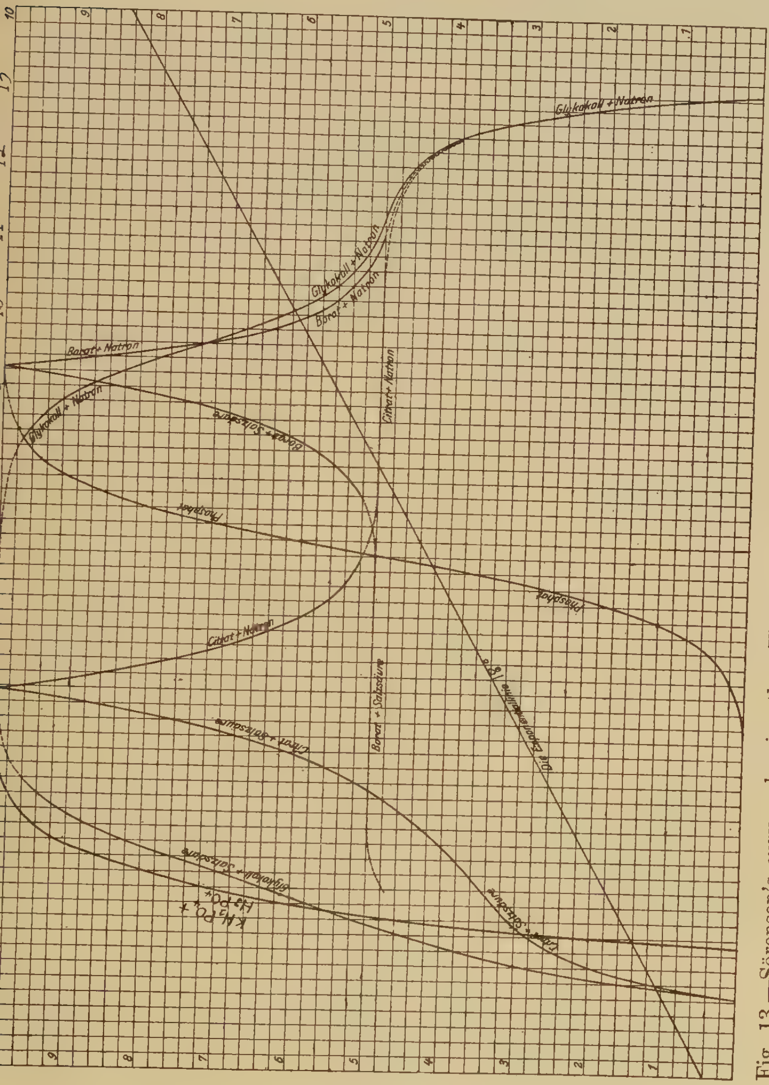


Fig. 13.—Sörensen's curves showing the pH of buffer mixtures. The curve for $KH_2PO_4 + H_3PO_4$ was determined by Dr. Medes.

adding varying quantities of KOH to a mixture containing equimolecular quantities of phosphoric, monochloracetic, lactic, acetic, and boric acids.

The accompanying chart (Sörensen—Fig. 13) indicates on the ordinate the proportions of stock solutions and on the abcissa the *p*H of the mixture. KH_2PO_4 denotes a solution of 9.078 gm. of the recrystallized anhydrous salt per liter. H_3PO_4 is a $\frac{M}{15}$ solution of phosphoric acid. Salzsäure is 0.1 *N* hydrochloric acid. Natron is 0.1 *N* sodium hydroxide free from carbonate. Borat is a solution of 12.404 gm. of recrystallized boric acid and 100 cc. *N* sodium hydroxide solution made up to one liter. Phosphat-phosphat denotes two different phosphates, the first one identical with the KH_2PO_4 mentioned above, and the second is 11.876 gm. of $Na_2HPO_42H_2O$ (air dried) to the liter. The organic acids decompose and are, therefore, not recommended.

It is sometimes more convenient to use borax than boric acid and NaOH. The following table shows the *p*H and per cent. of 0.05 *M* borax solution, the remainder being made up of 0.2 *M* boric acid solution.

*p*H	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9
Per cent. borax	2.5	2.7	3.2	3.9	5.0	6.1	7.4	9.9	10.6	12.7	15.1	17.7	20.5	23.7
*p*H	8.0	8.1	8.2	8.3	8.4	8.5	8.6	8.7	8.8	8.9	9.0	9.1	9.2	
Per cent. borax	27.3	30.9	35.2	39.7	44.4	49.3	54.7	60.7	67.4	74.5	81.5	89.2	96.8	

INDICATORS

Indicators are weak acids or bases. The mathematic relations of the latter are the reciprocal of those of the former. By the law of mass action the dissociation of an acid is expressed by the following formula:

$$\frac{[H^+] \times [A^-]}{[HA]} = K \qquad (6)$$

When a second acid is added its hydrogen ions are not distinguishable from the hydrogen ions of the first, so that $[H^+]$ is increased and $[A^-]$ must decrease because K is a constant. In other words, the addition of hydrogen ions lessens the dissociation of an acid. Since a strong acid produces a high concentration of hydrogen ions, its dissociation cannot be materially reduced by the addition of the relatively few hydrogen ions of a weak one. A weak acid, however, produces so few hydrogen ions that the addition of a strong acid with a relatively great number of hydrogen ions causes a marked decrease in the dissociation of the weak one. Any weak acid or base may be used as an indicator provided it produces ions which are easily distinguishable from the undissociated molecules. Those in common use are of two types—one with undissociated molecules that are colorless and ions that are highly colored, the other with undissociated molecules colored, usually a pale yellow, and ions brilliantly colored, but of a different region of the spectrum. Other explanations of these color changes have been offered and possibly several factors are involved, but at any rate the change of color seems to be a function of the hydrogen-ion concentration.

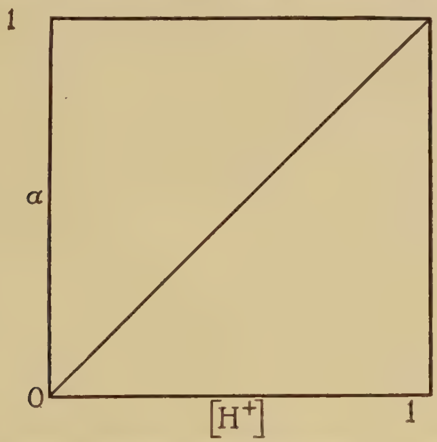


Fig. 14.—Curve showing variation of the dissociation, α, of an acid as related to the hydrogen-ion concentration.

The dissociation is determined, then, by the color. This is most easily done in a Duboscq colorimeter with an indicator such as phenolphthalein whose undissociated molecules are colorless. The amount of color represents the percentage of dissociation and can be read off directly by using a standard with 100 per cent. dissociation made by adding alkali to a portion of the indicator solution.

Indicators are acids of different strengths or different dissociation constants. In pure solutions of acids, the degree of dissociation, α, equals the hydrogen ion concentration, and therefore the curve shown in Fig. 14 holds true for all pure acid solutions except for hydrogen ions due to the dissociation of water.

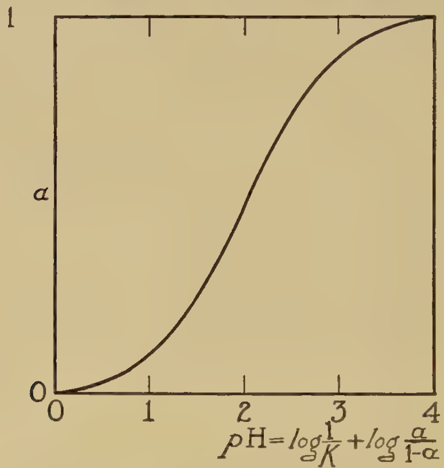


Fig. 15.—Curve showing the relation of a dissociation, α, of an acid and the pH.

If bases are present, the dissociation of the acid (anion) is represented by the formula:

$$\alpha = \frac{K}{K + [H^+]}$$

in which α is the degree of dissociation, K is the dissociation constant, and $[H^+]$ is the concentration of hydrogen ions. From this is derived: $pH = \log\frac{1}{K} + \log\frac{\alpha}{1-\alpha}$. By plotting the pH, or the logarithm of the reciprocal of the hydrogen ion concentration, against α the curve in Fig. 15 is obtained. It will be noted that the curve is steepest at 50 per cent. dissociation, showing that the most sensitive range of the indicator is at this *p*H. In the case of phenolphthalein, however, the eye obeys Weber's law in distinguishing colors and can detect a change from zero to 10 per cent. dissociation more easily than one from 90 to 100 per cent. The most sensitive range of this indicator in regard to ocular determination is somewhere between 0 and 50 per cent. dissociation, but only where the curve is fairly steep.

As it is difficult to draw this curve accurately, the scale may be changed on the ordinate so as to convert the curve into a straight line. The accompanying chart (Fig. 16) shows the range between 10 and 90 per cent. dissociation, which includes all the most useful and part of the less useful range. Basic indicators may be plotted on the same chart by using reciprocal values, and the more sensitive range will appear on the chart at a reciprocal of dissociation between 50 and 90 per cent.

In order to add a new indicator curve to the chart it is necessary only to find the *p*H at which the indicator is 50 per cent. dissociated, mark this point on the chart, and draw a line parallel to those already plotted. This is true provided the indicator is a monobasic acid. In case of a polybasic acid the straight line becomes curved. Michaelis claims that phenolphthalein behaves as a polybasic acid and has the following *p*H values for percentages of dissociation: 10 per cent., *p*H 8.95; 20 per cent., 9.2; 33 per cent., 9.35; 40 per cent., 9.5; 50 per cent., 9.7; 60 per cent., 9.9; 70 per cent., 10.1; 80 per cent., 10.3. For use with the Duboscq colorimeter it is necessary to obtain indicators whose undissociated molecules are colorless. The following is a list of these together with the *p*H at which they are 50 per cent. dissociated:

Indicator.	− log Ka = *p*H at 50 per cent. dissociation.
Alphanaphtholphthalein	8.3
Cresolphthalein	9.4
Phenolphthalein	9.7
2.6 Dinitrophenol	3.69
2.4 Dinitrophenol	4.06
Paranitrophenol	7.8
Metanitrophenol	8.35
Quinaldine red	2.6

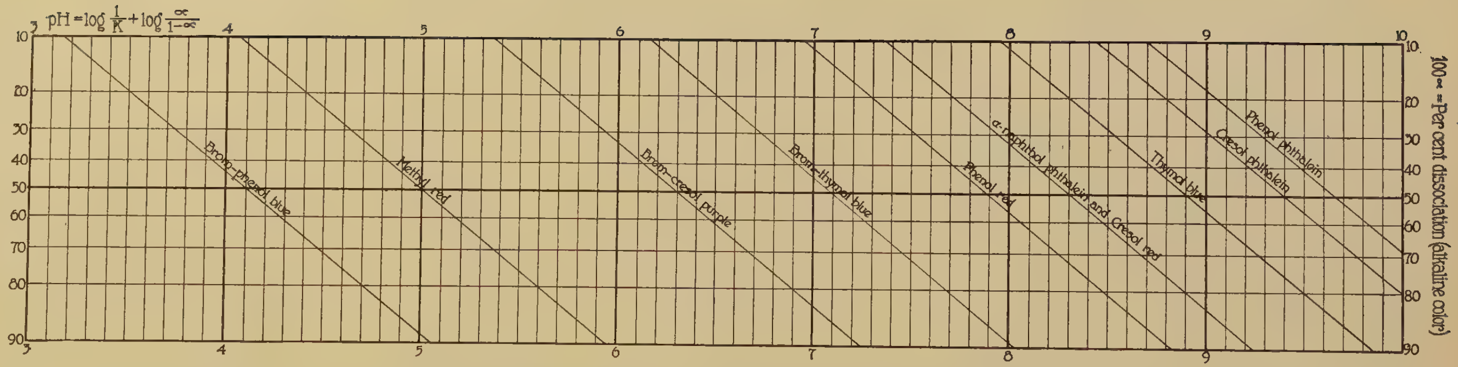


Fig. 16.—Curve showing the percentage dissociation of a number of indicators with change in *p*H. By changing the scale on the ordinate the curves were made straight. (From Journal of Biological Chemistry.)

Additional indicators are quinoline blue, tetrachlorphthalein, dinitrobenzoylene urea, and 4-6 dinitroguaiacol. Some with slightly colored molecules are p-dimethylaminophenyl-α-methylindolidinemethane and 4-nitro-6-aminoguaiacol. In case the undissociated molecules are colored, as with the yellow sulphonephthalein dyes, it is possible to modify the Duboscq colorimeter for their use. This was first done by Mines. Later Gillespie and Abbott independently studied the subject and used the same method in a large number of determinations. Mines, Abbott and Gillespie placed inside of the cup used for the standard in the Duboscq colorimeter an additional cup which could be moved up and down between the plunger and the regular cup. In the upper cup was indicator at 100 per cent. dissociation made by adding a drop of alkali to the solution, and in the lower one was indicator at 0 per cent. dissociation prepared by adding a drop of acid to the indicator solution. On the other side of the colorimeter was the unknown, colored with indicator which contained both undissociated molecules and ions, and was, therefore, mixed in color. By moving the additional cup up and down the percentage of ions to undissociated molecules in the standard could be changed and a color match obtained.

Various other devices, such as those based on dilution, have also been used. A very simple method for those indicators whose undissociated molecules are colored is to make up a series of tubes of equal bore containing the indicator in a buffered solution at different known *p*H values and compare them with the unknown by matching tubes. Kolthoff gives the following values for the Clark and Lubs series of indicators at 15°:

Indicator.	Dissociation constant.	*p*H at 50 per cent. dissociation.
Thymol blue (acid range)	2.4×10^{-2}	1.62
Bromophenol blue	1.0×10^{-4}	4.00
Methyl orange	2.0×10^{-4}	3.70
Methyl red	9.0×10^{-5}	4.05
Bromocresol blue (Bromocresol green)	8.0×10^{-6}	5.10
Bromocresol purple	8.5×10^{-7}	6.07
Bromothymol blue	8.4×10^{-8}	7.08
Phenol red	1.4×10^{-8}	7.85
Cresol red	6.5×10^{-9}	8.17
Neutral red	1.4×10^{-7}	6.85
Thymol blue	1.1×10^{-9}	8.96

When white light passing through a solution of an indicator is observed in a spectroscope, there may be a general absorption of the red and violet ends as well as one or more absorption bands

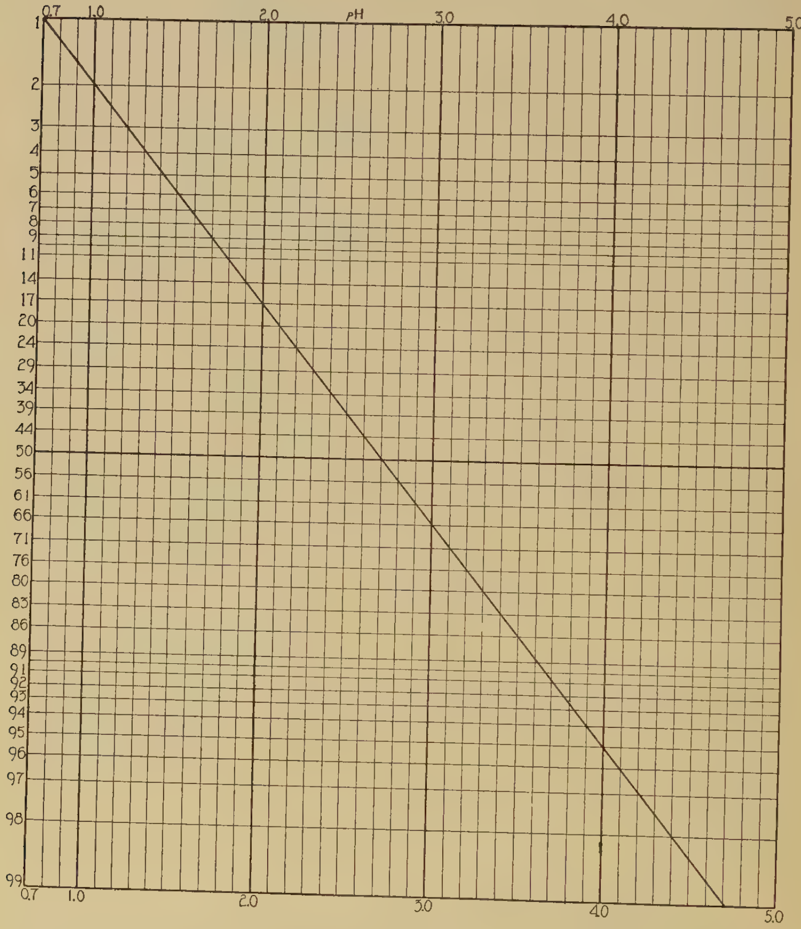
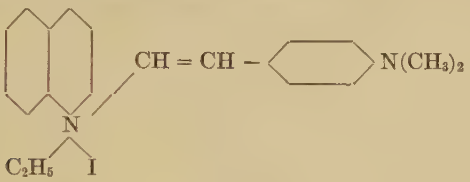


Fig. 17.—Dissociation of quinaldine red and pH. (From Journal of Biological Chemistry.)

in the intermediate region. For instance, methyl violet (krystall-violet 0) has one band at about 590 (D line) and a dimmer band at about 543 (between D and E). On change in pH the bands change in intensity and not in position. Brode determined *p*H by using a solution of an indicator of standard strength and measuring the intensity of one of the bands by means of the spectrophotometer.

The *p*H of gastric contents may be determined by means of the Duboscq colorimeter, using quinaldine red,



as an indicator (Fig. 17). The centrifuged gastric contents are measured and an equal measure of distilled water taken as a standard. The same amount of indicator is added to each. The percentage dissociation is determined by the percentage color. The *p*H is read from the following table:

Percentage dissociation	2	3	4	5	6	7	8	9	10
*p*H	1	1.2	1.3	1.4	1.5	1.6	1.65	1.7	1.74
Percentage dissociation	14	20	24	29	34	39	44	50	
*p*H	1.9	2.1	2.2	2.3	2.4	2.5	2.6	2.7	
Percentage dissociation	56	61	66	71	76	80	91	99	
*p*H	2.8	2.9	3	3.1	3.2	3.3	3.7	4.7	

Intermediate values are shown on the accompanying chart.

The *p*H of the urine usually comes within a range not covered by many indicators except very pale ones or those that slowly precipitate in colloidal form. It seems possible that 4-nitro-6-amino-guaiacol may be the best indicator for this purpose. This appears to be a polybasic acid, which from *p*H 0 to 4 gives an increasing (yet always pale) yellow color, and from *p*H 4.5 to 8.5 gives an increasing henna color. The method is as follows:

In the left-hand cup of a Duboscq colorimeter place 0.5 cc. of a 0.1 per cent. indicator and 10 cc. of urine. In the right-hand cup place 0.5 cc. indicator and 10 cc. 0.1 *N* NaOH solution. Adjust the left-hand cup to 20 mm., and hold under the right-hand cup a glass dish containing urine 20 mm. deep. Determine the percentage dissociation (percentage color) in the left-hand cup. In highly acid urines a color match cannot be obtained in this way. It is then necessary to place over the eyepiece a glass dish with some of the indicator in 0.01 *N* HCl. The following table gives the approximate *p*H at different percentages of dissociation:

*p*H............	4.6	4.7	4.8	4.9	5	6.1	5.2	5.3	5.4	5.5
Per cent. dissociation..........	3.0	3.5	4.0	4.5	5.5	6.5	8.0	9.0	11.0	13.0
*p*H............			5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3
Per cent. dissociation..........			15.0	17.0	19.0	22.0	25.0	29.0	33.0	37.0
*p*H............			6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1
Per cent. dissociation..........			42.0	46	50	54	58	62	66	70
*p*H............		7.2	7.3	7.4	7.5	7.6	7.7	7.8	7.9	8.0
Per cent. dissociation..........		74	77	80	83	85	87	89	91	92

The *p*H of the blood may be determined either with the hydrogen electrode or with indicators. In the hydrogen electrode it is better to use venous blood because it contains less oxygen. The blood should be drawn from the arm vein through a needle attached to a glass tube fitted with rather strong rubber tubing at the two ends. Into this glass tube is placed enough 30 per cent. potassium oxalate solution to make 0.1 per cent. potassium oxalate in the blood, and dry air drawn through until the oxalate solution dries in a thin layer on the glass. (In the case of certain animals a somewhat higher concentration of oxalate, up to 0.3 per cent., is necessary.) Blood is drawn into the tube in such amount that it overflows at the top. The portion that comes into contact with air is removed. The rubber tubes are then bent over and tied to the glass tube, which is rotated in the centrifuge until the corpuscles are precipitated. The glass tube is then placed in a clamp in a vertical position with the upper rubber tube attached to the hydrogen electrode and the lower tube attached to a mercury funnel. By the raising of this mercury funnel the plasma is forced into the electrode, leaving the corpuscles in the tube.

In the colorimetric determination of the hydrogen ion concentration of the blood it is necessary to dilute the blood-plasma about ten to twenty times, or else to dialyze it through a collodion sac in order that the blood-proteins be in not too high a concentration. Dilution makes very little difference in the hydrogen ion concentration. Dialysis also makes little change provided exposure to air does not occur. The concentration difference of H^+ due to the presence of a non-diffusible ion is too small to be significant. A good dialyzing apparatus contains very little air or none at all. The use of oil is not very efficient because CO_2 is more soluble in oil than in water or in air, but as convection currents in the oil are much slower than they are in the air, the oil acts as a stopper, though not nearly so efficiently as glass. Van Slyke uses a paraffin stopper.

A number of corrections have to be applied in diluting blood-plasma and determining the hydrogen ion concentration with indicators. In the first place the salt effect depends on the dilution. In the second place the color of the indicator depends somewhat on the temperature. As stated previously, the temperature has very little effect on the hydrogen ion concentration of blood or blood-plasma; consequently in a colorimetric determination of hydrogen ion concentration any change of color caused by variations in temperature may be ascribed to a change in the dissociation of the indicator, and a correction for this has to be applied. The most convenient way is to make all measurements at the same temperature, say at 20° or 25°, and then they will be comparable if not absolute. When the method is standardized with the hydrogen electrode the color of the indicator should be read at the same temperature at which all the color readings are to be taken. It is immaterial whether the hydrogen electrode is used at 20° or 25° or 37°, as the change in the pH through this temperature range is very slight. The usefulness of the Duboscq colorimeter is somewhat impaired by the possible loss of CO_2 from the cups, but this can be remedied by using a closed cup for the blood-plasma.

Cullen has standardized a method using phenol red as indicator. He dilutes the plasma twenty times with 0.9 per cent. NaCl solution, so that the salt error is about the same as that for the original plasma. As the method described above cannot be used with a two-color indicator, Cullen employs tubes of standard color in phosphate mixtures, and subtracts 0.225 from the reading to get the true pH. Lindhard has reduced the size of his apparatus. He uses 3 drops of blood, and by dialysis gets rid of the corpuscles as well as the protein.

Salt Error with Indicators.—The presence of salt in a solution to which an indicator is added causes an error in estimating the H^+ concentration. The magnitude of this error is rather difficult to state because all solutions contain more or less salt, and it is easier to estimate the difference between the salt error in two solutions than it is to find the absolute salt error. A great many determinations have been made with 0.2 *N* solutions of phosphates. There is considerable difference in salt error between 0.2 *N* and any other salt concentration—*i. e.*, Prideaux states the error due to 0.5 *N* NaCl as follows:

Salt.	Indicator.	Error in pH.
Phosphate	Paranitrophenol	+.15
	Alizarine sulphonic acid	+.26
	Rosalic acid	+.06
Borate	Phenolphthalein	+.12

According to this table, if salt is added to the solution the pH is changed in the + direction; that is to say, salt causes increase in dissociation of indicator whether acidic or basic. A great many salt errors were determined by Kolthoff. The error caused by addition of 0.5 *N* NaCl is as follows:

Indicator.	Error.
Thymol blue	+.17
Phenolphthalein	+.17
Brom phenol blue	+.35

To find the correct value the salt error should be subtracted from the apparent pH. With basic indicators, such as neutral red, the change is in the opposite direction and the correction should be added.

R. G. Wells has made a more thorough study of the error caused by addition of salt to the indicator, choosing cresol red. By comparing the errors caused by different amounts of salt and extrapolating for zero concentration, we may deduce the following for sodium chloride:

Per cent. NaCl	0.02	0.05	0.1	0.2	0.5	1	1.5	1.8
Error	0.03	0.08	0.11	0.16	0.21	0.26	0.39	0.3

Per cent. NaCl	2	2.5	3	3.5	4	10	20
Error	0.31	0.33	0.35	0.36	0.37	0.45	0.51

Phosphate mixtures that are ordinarily used are 0.2 normal, and they might be expected to cause an error somewhere around 0.3, so that this value would have to be subtracted from all the percentages given above in order to get values such as those of Kolthoff and Prideaux. A solution of 3 per cent. NaCl is 0.5 normal, and, if we were to subtract 0.3 from the error, it would equal 0.05, which is far from that found by Kolthoff and Prideaux. The explanation of this is that different buffer solutions behave differently. The cation has perhaps all of the salt effect or, rather, produces the salt error, whereas the anion has an antagonistic effect, but not enough to reverse the error, so that the two together produce less effect than one alone. Different anions, however, have different effects. Chloride has less antagonistic effect than phosphate, so that the salt error of 0.2 *N* sodium phosphate solution is less than that of 0.2 *N* sodium chloride. This, of course, leads to further complications. We should have to assume that the salt error of an 0.2 *N* phosphate solution is about 0.2. Then the difference between this solution and an 0.5 *N* sodium chloride solution would be 0.15, whereas Kolthoff gives it 0.17 for some phthalein indicators and 0.15 for others.

Now the standard indicator solutions are often made up in buffer mixtures, and it is found that temperature has very little effect on H ion concentration of a buffer mixture. However, when we add the indicator, the temperature change displaces the indicator color considerably. For instance, according to Kolthoff, a change in temperature from 18° to 70° changes the *p*H 0.4

except in more acid solutions, in which the change is less. This leads to the conclusion that the only safe path for the investigator is to use the hydrogen electrode to standardize his indicator-method under the conditions in which he is going to use it. For instance, in employing the method described above with the Duboscq colorimeter one point on the dissociation curve must be checked with the hydrogen electrode, using the same amount of salt in solution in the H_2 electrode as will be present in all the experiments, and then comparing it with the figures obtained by means of the Duboscq colorimeter at the temperature to be used in all determinations. If at any point in the experiments a change in salt concentration or temperature occurs, a new calibration must be made.

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PART II

PHYSIOLOGIC

CHAPTER VI

RADIANT ENERGY

THE most notable contribution toward our understanding of light was the work of Clerk Maxwell, who showed that light is an electromagnetic phenomenon. His work prophesied the production of the long electromagnetic waves which are now used in wireless telegraphy. These electromagnetic waves are very well understood. For instance, the wave given by the ordinary condenser type of antenna is a propagated electrical disturbance in the vertical direction accompanied by a magnetic disturbance in the horizontal direction, both at right angles to the line of propagation. In other words, the wave front is an electrical disturbance accompanied by a magnetic disturbance at right angles to it. Since these disturbances alternate in regard to a fixed point, the wave is described as undulatory—that is to say, like the graphic representation of a sine wave. If such a wave were of a certain wave length it would constitute what we are familiar with as plane polarized light. Ordinary light is made up of innumerable pulses, the planes of which are in all directions perpendicular to the direction of propagation.

The mechanism of the production of light has been somewhat elucidated by the discovery that *x*-rays are light rays of very short wave length. *x*-Rays are known to be made up of a series of pulses; in fact, it is found that the bombardment of a single molecule may give rise to a single pulse, and when the bombardment of a substance is very severe there will be innumerable pulses and an effect of light of very short wave length. The details of this process may be difficult to harmonize with the quantum theory.

It is deduced from the classical mathematics of electromagnetic phenomena that when a moving charged body is accelerated, some of its energy is propagated into space. The electrons are charged bodies moving about the atomic nuclei in circular or elliptic orbits. They are, therefore, accelerated toward the center, but it is postulated by Bohr that these are non-radiating orbits. Bohr assumes that radiation occurs only with a change in kinetic energy of an electron, that this change is accompanied by a change in the orbit, and that these changes are not continuous, but are step-wise, that is to say, of the magnitude of one or more quanta. When light falls on an atom, if its frequency is of a certain value, an electron absorbs a certain number of quanta of energy and moves to another orbit. With the absorption of this energy the energy content of the atom is increased. If the wave length is not of this value, the light is transmitted past the atom. Under certain circumstances the electrons that have been forced into orbits of higher energy content drop back into their old orbits, with the emission of light of definite wave length. Since quanta are radiated without decrease in energy with distance, J. J. Thompson postulated that each quantum travels along a string in the ether. It is known that when light falls on certain substances light of a different wave length may be emitted by the substance, but there is room for more data to be collected in this field. It seems that most of the data already collected concern the illumination of substances with non-visible light usually of short wave length, which causes an emission of visible light of longer wave length. Such emission may cease when the radiation ceases or it may persist for a longer time. It seems possible that in many cases electrons are thrown out of atoms and may affect other atoms.

It is a general rule that the shorter the wave length down to the ultraviolet region, the more easily the light is absorbed. For instance, the shortest wave that is transmitted by fluorite 1 mm. thick is 125 $\mu\mu$; by crystalline quartz, about 145; fused quartz, 180; common glass, about 315; air, 180, and water, 190. Ozone in the outer atmosphere absorbs the short waves up to about 291. Hence radiations of very short wave length would be absorbed even by air and water. The region of greatest absorption is in the ultraviolet, and hence ultraviolet rays are the most active chemically and physiologically. Rays both shorter and longer than these are absorbed less readily. For instance, *x*-rays have a wave length of from 0.01 to 0.1 $\mu\mu$ and the shorter ones are the so-called hard rays, which penetrate more deeply. Some gamma rays from radium are still harder, that is to say, shorter than *x*-rays.

Much interest has been aroused in regard to the action of light in causing photosynthesis in plants. It has been stated that after an atom absorbs a certain number of quanta of energy from light it is chemically more reactive, and that this is the basis of photochemistry. A number of experiments have been made to show that carbon dioxide dissolved in water can be changed into formaldehyde by ultraviolet light of specified wave length. This was first reported by Stoklasa and later by Baly. A paper by Spoehr failed to confirm this result. It is possible that the exact wave length, 220 $\mu\mu$, was not used by Spoehr, and that this wave length may be one that was absorbed rapidly by the quartz, or that waves shorter than 190 $\mu\mu$, that destroy formaldehyde, were present. Baly has shown that quartz becomes opaque to ultraviolet light by prolonged action of the light, and that it can be made transparent again by heating to a high temperature. Because, as is a well-known fact, formaldehyde in the presence of alkalies, particularly calcium hydroxide, and in the presence of ordinary daylight, polymerizes into sugar, it is thought that the whole process of photosynthesis has been outlined. Recently Baly brings evidence to show that glucose is formed directly from CO_2 and H_2O by action of light.

Baudisch has been studying photosynthesis of nitrogen compounds. With the photosynthesis of the carbohydrates and amino-acids the basis of the work in the laboratory of the green plant cell has been somewhat elucidated. The action of chlorophyll is that of a photosensitizer. Although we do not know the details of the action of such sensitizers, it is well known, particularly in the art of photography, that a chemical process that is effected by very short waves may be consummated by light of longer wave lengths if a sensitizer is added. The untreated photographic plate is what is known as a slow plate because it is most sensitive to ultraviolet rays, and these are absorbed particularly by the atmosphere and also by the glass of the lenses, and hence there are very few or none that reach the plate, and the visible light reaching the plate affects it relatively slowly. If, however, the plate is treated with eosin or other sensitizer it becomes more sensitive to longer waves and is, therefore, made into a rapid plate.

If the sensitizer is first exposed to light and then added to the reacting substances it is ineffective. They must be together during the illumination. The sensitizer is affected only by the light that it absorbs. It then transmits this energy to other atoms or molecules either in the form of light waves of very short wave length which are immediately absorbed and so escape detection, or in some other way, perhaps by shooting electrons. It seems possible that energy is radiated when certain substances in solution are oxidized. Meyerhof has shown that when one-fourth of the lactic acid in muscle is oxidized, part of the energy is used to transform the remainder into glucose.

Most of the processes in chemistry seem to be related more or less to oxidation and reduction. Oxidation of an atom consists in the loss of an electron. Thus an atom of metallic sodium on losing an electron becomes oxidized to a sodium ion. When this sodium ion combines with a chloride ion (reduced chlorine) to form a molecule of sodium chloride, the molecule now has its full share of electrons. If sodium chloride is dissolved in water the sodium chloride molecule may dissociate into sodium and chlorine ions. Therefore we suppose that even in the sodium chloride molecule the electron in question belongs to the chlorine and not to the sodium.

It is asserted that in crystals of a salt the atoms are in the ionic form, as the observations of Bragg by means of x-ray photography indicate. Perhaps even in the single molecule of an electrolyte the atoms are in the ionic form. When some substances are illuminated by light of given wave length their atoms may discharge one or more of these outer electrons. Since the valence of many substances, such as iron and copper, depends on the number of electrons they have lost, these electrons that are so easily lost are known as valence electrons. It is perhaps valence electrons that carry electric currents through metals. Not only may the surface of solid bodies lose electrons and therefore become oxidized under the influence of light, but many substances in solution may be similarly affected. Since solutions are always approximately electroneutral, whenever one atom is oxidized another is reduced, and hence when light produces an oxidation it also produces a reduction. Therefore the reduction of carbon dioxide in a plant is really a reduction only of the carbon and an oxidation of the oxygen, which escapes as oxygen gas.

Besides its action in photosynthesis light has a physiologic effect on both animals and plants. It was shown in 1905 by Hertel that whereas light of wave length 440 $\mu\mu$ required hours to kill bacteria, the same energy content of light of 280 $\mu\mu$ killed the same bacteria in seven seconds. Similar results were obtained with Paramœcia, and about the same values were obtained. Bacteria can then be killed by sunlight, but the action is much slower than by the ultraviolet light or by *x*-rays.

Our eyes perceive light of 380 to 760 $\mu\mu$ except in case of color-blindness. Light from 295 to 380 $\mu\mu$ is absorbed by the lens and transformed into visible light. Light of shorter wave length, which is very rare in sunlight but may be emitted by naked arcs and sparks and quartz-covered bulbs, is absorbed by the cornea and conjunctiva and produces inflammation. It is also absorbed by the skin. The short waves of sunlight may penetrate a millimeter of skin, but waves still shorter than this go down only about 1/10 millimeter. The short waves produce sunburn, but only the longer ultraviolet waves are supposed to produce tanning, and better tanning effect is obtained by sunlight than by some of the artificial ultraviolet lights.

Blood absorbs light over a wide range in the spectrum, but the very short waves cannot penetrate deep enough into the skin to effect direct cytolysis of the red cells. When, however, a sensitizer, hematoporphyrin, is present in the blood the longer waves cause changes that result in very toxic effects. This photosensitization was discovered by Raab, who found that the toxicity of acridin on Paramœcia depended on illumination. The presence of oxygen is necessary for these toxic effects. Chlorophyll is the chief photosensitizer in the living plant. Eosin has a photosensitizing effect when injected into the blood.

Light is effective in the treatment of disease. It has been shown that rickets and osteoporosis may be cured by the action of ultraviolet light or of sunlight that has not passed through glass. Rickets is a disease on which there is some difference of opinion, and therefore it is necessary for us to refer to the results of our own laboratory. There seems no question from these, as confirmation of work of Sherman and Pappenheimer, that in rickets the bone tissues are starving for phosphate. In osteoporosis there is a shortage of calcium. With the calcium shortage the bone tissue does not grow, and may even be absorbed, hence the need for calcium phosphate is reduced; but in phosphate starvation the bone tissue grows, and since there is no phosphate to mineralize this new bone, it grows at an increased rate, compensating by its bulk for its decrease in rigidity. This soft bone tissue is called osteoid, and is most noticeable in the growing areas of the bone of the young animal. Lack of Ca may prevent rickets by stopping bone growth. If the animal is given cod-liver oil both calcium and phosphate are better retained, perhaps the path of excretion is blocked, and rickets and osteoporosis are relieved. There is a report by Steenbock, Black, and Nelson that when some fats that do not act like cod-liver oil are exposed to ultraviolet light they acquire a potency in the treatment of rickets and osteoporosis. Kugelmass and McQuarrie have reported that substances curative of rickets emit ultraviolet rays in the presence of oxygen and suggest the following reaction:

$$\text{Oxygen} + \text{Rickets-curing Substances} \rightleftarrows \text{Oxy-Substances} + \text{Ultraviolet Rays}$$

According to them this reaction is a reversible one, oxygen being liberated when oxidized cod-liver oil is exposed to ultraviolet rays.

It seems possible that ultraviolet light penetrates only about 1 millimeter of our skin and causes some chemical change there, resulting in the production of a substance that is carried by the blood to all parts of the body and influences the calcium phosphate metabolism. The action of light in curing rickets and osteoporosis is accompanied by tanning of the skin. This tanning action is produced only by the ultraviolet light of rather long wave length, which can penetrate relatively deep into the skin, and it seems that these waves are of therapeutic value in general.

Light has been used chiefly in the cure of tuberculosis of the skin, known as lupus. Finsen established an institute for the study of such a process, and has been very successful in the treatment of lupus. He asserted also that eczema and acne are sometimes cured by light, but these two diseases are cured more rapidly by very short waves represented in *x*-rays. *x*-Rays, however, although of very short wave length are sometimes of great penetrating power, and there is danger of affecting deeply placed organs and tissues, particularly spleen, lymph-nodules, bone-marrow, and gonads. For instance, the embryo in the uterus is killed by *x*-rays without injuring the adult tissues. The male may be temporarily sterilized by raying the testes. As a rule rapidly growing tissues are more affected, and for this reason *x*-rays are used in the treatment of cancer, being very destructive to cancer cells.

The gamma rays of radium are *x*-rays, and hence radium is also used for this purpose. It can be placed in tubes and held on by bandages or introduced into inner cavities. Owing to the cost of radium the application is usually made in the form of very small glass tubes filled with radium emanation and stuck into the cancerous tissue at equally spaced intervals. Since the action is very destructive and the tissue is finally removed, the removal of the glass does not require any great amount of care. In this case the alpha and beta rays add to the effect of the gamma rays.

It has been shown that besides lupus other forms of tuberculosis may be treated with sunlight. The so-called surgical types are treated with better results by sunlight than they are by surgery. Light increases the formation of granulation tissue in wounds. This tissue is at first red, but later turns white. It has been asserted that too much light may cause an overgrowth of the scar tissue, which bulges out of the wound and remains red for a long time.

Regarding the different sources of light, the choice is one of wave length. Sunlight, whether on the Alps or at much lower levels, does not contain rays shorter than 291 $\mu\mu$, but the angle at which the rays strike the atmosphere determines the quantity of the short rays that penetrate; therefore the maximum radiation, particularly of the ultraviolet rays, occurs only when the sun is directly overhead, therefore the time of day, season, and latitude are very important. Altitude, by eliminating the lower regions of the atmosphere, increases the quantity of ultraviolet light, but does not affect the presence of waves shorter than 291 $\mu\mu$.

Since light may cause oxidation of an atom it seems unnecessary to look for a further explanation of the destructive action of light. It has been shown that proteins may be coagulated by ultraviolet light. Bovie has studied especially light of the so-called Schumann region of wave length from 125 to 200 $\mu\mu$. A layer of air 1 cm. thick or a layer of water 0.5 mm. thick absorbs all of these rays except the longer Schumann rays, and fluorite is the only solid that transmits them all. Bovie has shown that some proteins which are not directly coagulated by illumination may be so sensitized that their coagulation by other agents is accelerated. It seems, however, that we may fall into error in making the statement that albumins are transformed into globulins by the action of ultraviolet light, since there is much that we do not understand about the constitution of these substances. Under some circumstances Bovie has found that illumination may retard the coagulation of some proteins. Friedberger and Scimone assert that ultraviolet radiation tends to destroy the amboceptor in hemolytic serum.

BIOLUMINESCENCE

Perhaps all living organisms emit visible light when illuminated by ultraviolet light. Some living organisms, however, emit light at will. At any rate, there may be a nervous mechanism controlling the light emission, and since the firefly, for instance, may emit light on a dark night, we may assume that it is not a case of change of wave length, the firefly not being at the time exposed to ultraviolet light. We are, however, ignorant of the method of transferring energy from one atom to another in chemical reactions, and Perrin presents the hypothesis that all chemical reactions are accompanied by the emission and absorption of light. Oxygen is necessary for the production of light by the firefly, which can probably shut off the light at will by shutting off the oxygen—for instance, by contracting the tracheal tubes in luminous organs. Harvey has studied bioluminescence for a number of years and isolated the substance luciferin, which when oxidized produces the substance oxyluciferin. Luciferase, water, and oxygen are necessary for the oxidation of luciferin to oxyluciferin. Light is emitted during the oxidation process. Certain catalyzers aid the reduction of oxyluciferin to luciferin.

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CHAPTER VII

ATOMIC STRUCTURE AND PHYSIOLOGIC ACTION

The physiologic as well as the physical and chemical properties of ions bear some relation to their position in the periodic table. Chemical properties are determined by atomic number rather than by atomic weight. Isotopes of the same atomic number but different atomic weights are so closely related chemically as to make separation nearly impossible.

The elements when arranged serially according to atomic numbers are found to fall into the periods of the table of the elements, which repeat certain properties related to valence. In the zero group of the periodic table helium, neon, krypton, and xenon have valences of zero and make no chemical combinations. In the first group lithium, sodium, potassium, rubidium, and cæsium have unit valences in aqueous solution, becoming univalent positive ions when oxidized by the removal of an electron. In the second group beryllium, magnesium, strontium, and barium have valences of two, becoming divalent positive ions. In the third group boron, aluminum, scandium, yttrium, and lanthanum have valences of three, becoming trivalent positive ions. In the fourth group carbon, silicon, germanium, and tin have valences of four, which may be positive or negative. Carbon also exhibits to a greater extent than any other element the property of uniting with other atoms like itself, and thus forms the long chains which make possible the enormous molecules found in protoplasm. In the fifth group nitrogen, phosphorus, arsenic, and antimony have negative valences of three and form acids. In the sixth group oxygen, sulphur, selenium, and tellurium have negative valences of two and form acids. In the seventh group the halogens, fluorine, chlorine, bromine, and iodine have unit valences, becoming negative ions on reduction in aqueous solution.

The physiologic properties of the elements that form ions independently—*i. e.*, the alkali and alkaline earth metals and the halogens—have been compared with their effects on the physical properties of the water in which they are dissolved. The order of the alkali metals in the periodic table is:

Li, Na, K, Rb, Cs

With the exception of Li, their electrolytic solution tensions increase in this order (become more positive from left to right). Other properties that increase in this order are their atomic weights, coefficients of expansion, compressibilities, atomic volumes, ionic speeds, adsorbability and effectiveness in reversing the charge on or precipitating or shrinking negative colloids or accelerating the hydrolysis of esters by acids.

Some properties decrease in this order—*i. e.*, their melting-points, the viscosity of their aqueous solutions, and their effectiveness in salting-out dissolved gases, non-electrolytes, and positive colloids, as well as their effectiveness in accelerating the hydrolysis of esters by bases.

With the possible exception of Li, their toxicity and effectiveness in decreasing the rate of settling of erythrocytes increases in the order above. Sodium salts are difficult to purify, but when sodium chloride, for instance, is in pure aqueous solution it is toxic. Therefore there may be some doubt that Li is an exception in regard to its toxicity.

Of the alkaline earth metals the properties of beryllium have been least investigated, the others are arranged in the order:

Mg Ca Sr Ba

The following properties increase in this order: atomic weight, electrolytic solution tension, ionic speed, adsorbability and effectiveness in accelerating the hydrolysis of esters by acids, and reversing the charge on negative colloids. Their effectiveness in accelerating the hydrolysis of esters by bases decreases in the order above. Their toxicity increases in the same order.

The order of the halogens in the periodic system is

F, Cl, Br, I

The properties that increase in the order above are atomic weight, atomic volume, melting-point, adsorbability and effectiveness in salting out positive colloids, and increasing the hydrolysis of esters by acids and maintaining the negative charge on porous diaphragms. Their effectiveness in salting out gases, non-electrolytes, and negative colloids decreases in the order above.

In physiology this order of halogens is called the Hofmeister series (which includes complex anions also). Fluorides are intense poisons on account of the precipitating power of F^- on Ca^{++}, and therefore must be omitted from the series. The effectiveness of the remaining halogens decreases in the same order in restoring the irritability of muscle removed from isotonic sugar solution, and increases in the same order in producing cytolysis, hemolysis, and dissolution of cilia, and in decreasing the rate of settling of erythrocytes.

It was shown by Mathews that the physiologic properties of an ion depend on its electric state (valence) and electric stability (electrolytic solution tension). The valence of some elements depends on their state of oxidation, that is to say, they are capable of more than one state of oxidation, and hence may change their valence. The toxicity of the ion depends on its valence, and hence the toxicity of Fe^{++} and Fe^{+++}, for instance, may not be the same. The low toxicity of iron, aluminum, or manganese is due, however, to the low solubility of the phosphate, except at hydrogen ion concentrations greater than exist in the blood or cell interior. In order to study the toxicity quantitatively it is necessary to determine the concentration of the ions at their point of attack on the living cell. The determination of the electrolytic solution tension is very difficult, as shown by the fact that the newer values may vary considerably from the older ones. The most reliable values are those calculated from the electrode potentials of dilute amalgams. The purity of the metal, cleanliness of the amalgam surface and concentration of the amalgam, and concentration of the ions in solution must be measured very carefully if accurate results are to be obtained.

An attempt is made in the following series to arrange metals in order of their electrolytic solution tensions: Al^{+++}, Mn^{++}, Zn^{++}, Fe^{++}, Cd^{++}, Tl^{+}, Co^{++}, Ni^{++}, Sn^{++}, Pb^{++}, Fe^{+++}, H^{+}, Cu^{++}, Bi^{+++}, Sb^{+++}, Hg^{++}, Ag^{+}, Pd^{++}, Pt^{++}, Au^{+}. Mathews found the order of increasing toxicity of salts of metals on fundulus eggs to be Mn, Fe, Co, Ni, Zn, Pb, Cd, Cu, Hg, Ag, Au. He did not determine the ion concentrations, but it is well known that hydrolysis occurs in solutions of some of these salts. The similarity of the two series is very striking. All of the ions of the series are very toxic, and yet these elements exist in soils. All that saves the life of plants growing in the ground is the slight solubility of the heavy metals at the hydrogen ion and phosphate ion concentrations existing in soils. Since this matter is taken up in detail under the section on Hydrogen Ion Concentration it will not be considered in detail here.

The toxicity of the different ions is not always additive, but sometimes antagonistic. Whereas Na^{+} is toxic in pure solution, this toxicity is antagonized by a small amount of Ca^{++} or some other ions (see section on Permeability).

Sea-water contains small quantities of all the heavy metals, whose effects are probably neutralized by the high concentration of Na^{+}.

The heavy metals form poorly dissociated compounds with proteins, fatty acids, and carbohydrates. These protein compounds swell less in water than do the unaltered proteins, hence heavy metals such as chromium are sometimes used in tanning. Chrome leather is green and may be said to be overtanned. Usually a little sulphuric acid is purposely left in it to counteract the effect of the chromium and cause it to swell to a slight extent.

The immediate effect of Al^{+++} and Pb^{++} on erythrocytes seems to be a tanning of the surface, although by this term is merely meant union with the metal, as the union may be with fatty acid and not necessarily with protein.

One ion may be substituted for another in a solution bathing the surfaces of living cells provided its concentration and the concentrations of the other ions are so adjusted as to preserve the physiologic ionic balance. Thus Li^{+} may be substituted for

Na^+ (Overton). Such substitutions in the human body are made difficult by the loss of the ion in question through the kidneys. The substitution of Br^- for Cl^- produces toxic effects upon the nervous system before all of the Cl^- has been removed from the blood. A fuller discussion of ions in the blood is found in Chapter XI.

Herbst showed that Na^+, K^+, Ca^{++}, Mg^{++}, Cl^-, SO_4^{--} and HCO_3^- are necessary for the development of sea urchin eggs into larvæ. Part of the K^+ could be substituted by Rb^+ or Cs^+ and part of the Cl^- by Br^-.

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CHAPTER VIII

THERMOCHEMISTRY IN THE LIVING BODY

Chemical reactions are accompanied by evolution or absorption of heat. Those accompanied by evolution of heat are called exothermic, and those accompanied by absorption of heat are called endothermic. All chemical reactions, so far as is known, are either exothermic or endothermic except possibly the formation of one optical isomer from the other. The reactions in living matter are largely of two types: (1) oxidation and reduction, and (2) hydrolysis, and synthesis with the loss of water. In the last type energy changes are very slight. Heat produced in living matter is due chiefly to oxidation. This heat is liberated in exothermic chemical reactions or is the algebraic sum of the heat liberated in both exothermic and endothermic chemical reactions. However, other reactions, some of which are endothermic, cannot be ignored. The unit of heat is the large or kilogram Calorie (Calorie) which is the heat required to raise 1 kilogram of pure water from 15° to 16°.

In order to find the heat of combustion of a chemical compound the heat of formation of the substance in question must be deducted from the heat of combustion of the elements contained in it. The physical state of the elements, whether gaseous, liquid, or solid, and in some cases whether crystalline, amorphous, or in one of the several allotropic forms, must be defined, since in passing from one chemical state to another energy changes are involved. These changes, however, are slight as compared with the heat of combustion or heat of formation. For instance, the heat of fusion of H_2O is 1.4 Calories per mol, and of other substances is never more than 0.005 Calories per mol, and the heat of vaporization of water is 9.7 Calories per mol, while that of other substances is very much less. In the following equation *solid* is abbreviated by (*s*), *liquid* by (*l*), and *gaseous* by (*g*). In the ordinary equation one mol of a compound is the unit considered except where otherwise indicated, as, for instance, in the food-stuffs where the molecular weight has not always been determined accurately, and a gram is considered the unit.

The heats of combustion of solid carbon and gaseous hydrogen may be shown by the following equations:

$$C\ (s) + O_2\ (g) = CO_2\ (g) + 94.3 \text{ Calories}$$
$$2H_2\ (g) + O_2\ (g) = 2H_2O\ (g) + 136.6 \text{ Calories}$$

Methane (CH_4) has a heat of combustion of 213.8 Calories; *i. e.*,

$$CH_4\ (g) + 2O_2\ (g) = CO_2\ (g) + H_2O\ (g) + 213.8 \text{ Calories}$$

This is 17.1 Calories less than the heats of combustion of C (*s*) and $2H_2$ (*g*) added together. This difference represents the heat given out in the formation of methane. In other words, the calorific values of carbon in solid form and hydrogen in gaseous form are together greater than the calorific value of methane. The following table gives the heat of formation per mol (from the chemical elements), the heat of combustion per mol, and the heat of combustion per gram of various carbohydrates and organic compounds:

KILOGRAM CALORIES

	Molecular weight.	Heat of formation per mol.	Heat of combustion per mol.	Heat of combustion per gram.
Arabinose	150	259.4	557.1	3.71
Glucose	180	302.6	677.2	3.76
Fructose	180	302.1	675.9	3.75
Sucrose	342	535.6	1355	3.96
Lactose	342	535.6	1351.4	3.95
Dextrin	162	243.6	667.2	4.12
Inulin	162	231.4	679.3	4.19
Starch	162	225.9	684.9	4.23
Stearic acid	284	222.6	2682	9.45
Glycerol	92	165.6	397.1	4.32
Ethyl alcohol	46	69.9	325.7	7.08

It may be noticed that the heat of combustion per gram of polysaccharides is more than that of disaccharides and still more than that of monosaccharides. This is due to the fact that in changing from polysaccharides to disaccharides and then to monosaccharides, water, which has no calorific value (being completely oxidized), is taken up. Water increases the weight and therefore decreases the calorific value per gram.

In the combustion of the substances listed above the end products are CO_2 and H_2O, and are the same whether burned inside the body or outside, but where incomplete combustion takes place not all the heat is liberated, and it is necessary to know the calorific value of the end products in order to calculate the heat of combustion of the original substance. In the living body protein is not completely burned, urea and other substances being formed. For this reason the heat of combustion of protein is smaller when burned in the body than when burned outside, and can be calculated only by complete analysis of the end products as well as of the initial ones. Possibly these calculations might be eliminated by direct measurements of heat given off during the burning of protein in the animal body, but this method is open to various experimental errors. In the first place, the end products may not always be the same; for instance, in the burning of proteins in the body the end products vary according to whether body protein is being burned, as in starvation, or whether a diet of pure protein has been fed, or whether other substances are fed along with the protein. In any case the protein burned must be calculated from the nitrogen in the urine, and here also a second source of error may arise. For instance, in starvation the burning of body protein produces 3.84 Calories of heat per gram of protein; after eating purified meat-protein 4.42 Calories per gram are produced, and after eating meat which contains also some fat and nitrogenous extractive, the statement is made that 4 Calories per gram of meat protein are given off; but just how much protein has been burned and just how much of the heat produced is due to this protein seems doubtful. A third source of error lies in the fact that the calculation of the protein from the nitrogen in the urine is usually done by multiplying grams of nitrogen by the average factor 6.25 to obtain the number of grams of protein burned. The following table will show what errors may arise:

Protein.	Per cent. N.	Per cent. C.	Factor.
Legumin	18	51.7	5.56
Fibrin	17	52.7	5.90
Meat protein (mixed)	16.65	52.4	6.00
Ovovitellin	16	51.6	6.25
Serum globulin	16	52.7	6.25
Zein	16	55	6.25
Egg albumin	15.5	52.75	6.45

The factor in the proteins here given varies from 5.9 to 6.45. The method of obtaining this protein factor is to determine directly the calorific value of the urine, and here a fourth source of error appears. The calorific value of the urine varies, 1 gram of urinary nitrogen on a mixed diet being equal to 8.09 Calories, and on a high carbohydrate diet 11–13 Calories (because of the presence of formic acid, Dakin). The protein lost in the feces does not introduce an error when the protein is calculated from the urinary nitrogen, but when it is calculated from the protein fed we have to distinguish the protein in the feces from undigested food proteins and proteins from the secreted mucin and bodies of bacteria. In ordinary cases the nitrogen in the feces is an index of the calorific value of the feces on the assumption that protein alone is burned. In some cases formic acid appears in the feces and increases the total calorific value of the feces. When we subtract the weight of the ash and water from the feces, the remainder, produced on certain high protein diets, is 6.852 Calories per gram; on a meat diet, 6.127 Calories per gram. Rubner's figures for the average diet is 6.2 Calories per gram.

The heat value of the protein burned in the body varies with the proteins as shown by direct determinations. According to Rubner, casein produces 4.4 Calories, whereas meat protein produces 4.233 Calories per gram, and vegetable proteins 3.96 Calories per gram. Rubner arbitrarily takes the value of 4.1 Calories per gram for protein. In severe diabetes not all of the protein is burned in the body, but about 58 per cent. of it is converted into sugar which is eliminated in the urine, thus further decreasing the calorific value of the protein.

Fats produce more heat than carbohydrates, and produce the same amount whether burned outside the body or inside under normal conditions of health; but in starvation or severe diabetes they are not completely burned, but the products stimulate the metabolism and a portion is eliminated as beta-hydroxybutyric acid. Olive oil produces 9.384 Calories per gram; the fat of adipose tissue, 9.372; butter fat, 9.179, the lower value for butter fat being due to the presence of lower fatty acids. Rubner takes the arbitrary value of 9.3 Calories per gram for fat.

The instrument for measuring the capacity factor of heat energy is called a calorimeter. Such an instrument may vary all the way from a very simple form, commonly used for determining the heat of reaction of two chemical compounds, to the elaborate respiration chambers. The simplest types consist of two concentric chambers insulated from each other by an air jacket and covered by a vulcanite covering through which passes a thin-walled test-tube, a thermometer, and a ring stirrer. This inner chamber is filled with water. In order to find the heat of reaction of substances introduced into the test-tube the capacity of the calorimeter must first be determined. The capacity of the apparatus is the number of calories required to raise the temperature of the water in the calorimeter 1 degree.

The instrument in general use for the determination of heat of combustion of organic compounds is called the bomb calorimeter. The substance is placed inside a steel bomb with non-corrosive lining and filled with compressed oxygen and ignited by means of an iron wire heated by an electric current. The lining is made of glass-enamel, platinum, chromium-nickel-steel, or other alloy. The bomb lies immersed in a measured quantity of water inside a Dewar flask. The water surrounding the bomb is stirred with a stirrer that produces very little friction or none at all. The mass of water in the calorimeter being known, and its temperature having been read before and after combustion, the quantity of heat evolved may be calculated. Since there are metal parts in the bomb the heat capacity of the apparatus must be measured and the heating effects of the electric current and that due to combustion of the iron must be subtracted from the total. In some cases a platinum wire may be used, but there is danger of melting it or alloying it with phosphorus or base metals unless it is placed to one side of the substance to be burned.

Heat of combustion of substances in the body may be determined either by direct or by indirect calorimetry. By the direct method the individual is placed in a chamber with suitable devices for measuring the heat evolved. In the indirect method the heat evolved is estimated from the end products of metabolism. In the latter case the sources of error are more numerous, as has been partially explained in the paragraphs above. In case the direct method is used the indirect is usually employed at the same time, and exceedingly great accuracy in interpretation of metabolic processes may be attained.

In indirect calorimetry the heat production may be estimated either from the oxygen consumed during a given period or from the carbon dioxide given out, or both. In the oxidation of a carbohydrate:

$$C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O,$$

the O_2 consumed equals the CO_2 given out in molal concentrations, and the respiratory quotient (R. Q.) equals one.

$$\text{R. Q.} = \frac{CO_2}{O_2} = 1$$

When a fat is burned the reaction may be written

$$C_3H_5(C_{18}H_{33}O_2)_3 + 80\ O_2 = 57\ CO_2 + 52\ H_2O$$

$$\text{R. Q.} = \frac{CO_2}{O_2} = 0.71$$

If carbon dioxide output alone is taken as the basis of measurement, a considerable error may occur because of guessing at the R. Q. The calorific value of a liter of carbon dioxide when carbohydrate is burned is 5.05 Calories, and when fat is burned, 6.61 Calories. If oxygen alone is measured, the error due to guessing at the R. Q. is less, the calorific value of a liter of oxygen when carbohydrate is burned being 5.05 Calories, and when fat is burned, 4.69. In the latter case the error of calculation is scarcely greater than the error of the experiment.

Another source of error lies in determination of the oxygen intake. When apparatus of the closed system type is employed, oxygen is either added to the system quantitatively as it is withdrawn, or its volume is measured by the amount of fall of the bell of the spirometer containing oxygen. In either case corrections must be made for temperature, pressure, and vapor tension. In cases where oxygen is determined volumetrically and carbon dioxide gravimetrically slight errors in the R. Q. are likely to occur, since both are not affected alike by variations from standard conditions.

To determine the proportion of protein, carbohydrate, and fat burned for a given respiratory quotient, the non-protein respiratory quotient must first be calculated. This is obtained by deducting from the total oxygen absorbed the oxygen required to oxidize protein, and from the total carbon dioxide that derived from protein. From the following formula the respiratory quotient for the oxidation of protein in the body may be obtained:

$$C_{72}H_{112}N_{18}O_{22}S \text{ (albumin)} + 77O_2 = 63CO_2 + 38H_2O + 9CO(NH_2)_2 + SO_3$$

$$\text{R. Q.} = \frac{CO_2}{O_2} = \frac{63}{77} = 0.82$$

The O_2 required to oxidize the protein may be calculated in liters.

$$\text{Urinary N (grams)} \times 6.04 = O_2 \text{ (liters)}$$

and the CO_2 given off may be calculated:

$$\text{Urinary N (grams)} \times 4.88 = CO_2 \text{ (liters)}$$

Then, dividing the non-protein CO_2 by the non-protein oxygen, we find the non-protein respiratory quotient. From the non-protein respiratory quotient the amounts of carbohydrate and fat which have been burned may be calculated. These calculations are rather complicated, and in order to simplify them the following table is reproduced (modified from Lusk):

Non-protein Metabolism

1 liter of Oxygen is Equivalent to

Non-protein respiratory quotient.	Grams.		Calories.
	Carbohydrates.	Fats.	
.707	0.000	0.502	4.686
.71	0.016	0.497	4.690
.72	0.055	0.482	4.702
.73	0.094	0.465	4.714
.74	0.134	0.450	4.727
.75	0.173	0.433	4.739
.76	0.213	0.417	4.751
.77	0.254	0.400	4.764
.78	0.294	0.384	4.776
.79	0.334	0.368	4.788
.80	0.375	0.350	4.801
.81	0.415	0.334	4.813
.82	0.456	0.317	4.825
.83	0.498	0.301	4.838
.84	0.539	0.284	4.850
.85	0.580	0.267	4.862
.86	0.622	0.249	4.875
.87	0.666	0.232	4.887
.88	0.708	0.215	4.899
.89	0.741	0.197	4.911
.90	0.793	0.180	4.924
.91	0.836	0.162	4.936
.92	0.878	0.145	4.948
.93	0.922	0.127	4.961
.94	0.966	0.109	4.973
.95	1.010	0.091	4.985
.96	1.053	0.073	4.998
.97	1.098	0.055	5.010
.98	1.142	0.036	5.022
.99	1.185	0.018	5.035
1.00	1.232	0.000	5.047

In the first column of the table we find a figure equal to the non-protein respiratory quotient. Trace this line of the table horizontally to the right and in the second column will be found the number of grams of carbohydrate that have been burned for each liter of non-protein oxygen, in the third column the number of grams of fat burned for each liter of non-protein oxygen, and in the fourth column the number of Calories produced for each liter of non-protein oxygen. Protein Calories are determined by multiplying the grams of urinary nitrogen by 26.51. This added to the non-protein Calories gives the total Calories for the period.

It is very well to know how many grams of carbohydrate and fat have been burned, not only from the point of view of determining whether the metabolism may be normal or not, for when it is very abnormal the calculations mean very little, but also any absurdity in the results shows that the experiment is worthless. The subject cannot burn less than zero grams of carbohydrate or fat. In some cases where it is assumed that no carbohydrate is burned, these calculations may show some actually to be burned. Of course, if any beta-hydroxybutyric acid is eliminated, that reduces slightly the accuracy of the calculation and lowers the respiratory quotient for the burning of fat from 0.707 to 0.669. Transformation of glycerol into carbohydrate and its elimination in diabetes would cause an error. Storage of fat due to transformation of carbohydrate requires no oxygen, but produces some CO_2, and hence it leads to a large error; but most of the determinations have been done so as to eliminate such errors.

Very little oxygen is held in the blood and tissues of the body. Certain amounts of CO_2 are held, and any change in the CO_2-holding power of the blood or tissues from the beginning to the end of the experiment would cause an error. In the chill accompanying fever the temperature of the surface of the body is lower than usual and that of the interior higher than usual, and this produces a change in the heat storage of the body. This may introduce considerable error in the calculation of the heat produced.

In some types of calorimeter used in indirect calorimetry the spirometer is filled with oxygen and the subject breathes into and out of this spirometer, the CO_2 being absorbed; therefore the depression of the bell of the spirometer is the measure of the oxygen taken by the patient. If, however, the lung volume is different at the end from that at the beginning of the experiment, an error will arise. It is very desirable in such cases to have a graphic record of the rise and fall of the spirometer bell showing the time relations to see whether the respirations are regular. A number of spirometers now in use are designed for use with the recording drum. If the CO_2 absorption is defective, CO_2 will accumulate and cause a very marked increase in respiration rate and entirely throw off the result, but even if this does not occur, various influences change the respiration. By the graphic record, in choosing a time when the respirations are regular, the rate of utilization of oxygen may be determined and the amount calculated for the total period.

In the portable type of apparatus the CO_2 is usually not determined because a container filled with soda lime sufficient in amount to absorb all the CO_2 produced by one person weighs about 2 kilograms. Besides this, the water given off by the soda lime must be weighed and the water absorption apparatus is weighed with the soda lime tank, increasing the weight still further. It would require a balance sensitive enough to weigh the CO_2 produced, yet capable of carrying this enormous load. Such a balance is very expensive and usually is not at hand. Sometimes ascarite is employed instead of soda lime. Ascarite is asbestos containing NaOH, and by its use it may be possible to reduce the weight of the apparatus.

Another method is to absorb the CO_2 in standard barium hydroxide solution. The following is a description of an arrangement used in this laboratory: A mask is fitted to the subject's face; from this mask two tubes lead out, one directly to the spirometer, admitting oxygen from the spirometer to the mask; the other tube passes through a 3-liter glass jar containing an accurately measured quantity—for instance, 1 liter of half-normal barium hydroxide solution colored with phenolphthalein. The $Ba(OH)_2$ solution is made by adding 1 N NaOH solution to an equal volume of $BaCl_2$ solution. The tube passing into the jar extends into the center of a centrifugal blower which drives the expired air into the jar. The lower part of this blower acts as a stirrer, which not only stirs the solution, but sprays it up at the rate of about 500 cc. or more per second, throwing a fine spray in all directions through the air in this jar. It is found necessary to spray this at an enormous rate in order to absorb all of the CO_2. Another tube passes from this jar to the spirometer. As the subject breathes the CO_2 is absorbed in the jar as barium carbonate, and oxygen passes from the spirometer bell to the subject. The oxygen is determined by the fall in the spirometer bell from the moment the stop-watch is started at the beginning of the experiment, and the CO_2 is determined by stopping the experiment at the instant the phenolphthalein turns colorless. The oxygen is measured while saturated with water vapor at room temperature and must be reduced to standard conditions—*i. e.*, to 0°, 760 mm. barometric pressure, and dryness—by the usual methods. The CO_2 is determined by multiplying the liters of half-normal barium hydroxide by 5.6 to get the liters of CO_2 under standard conditions.

The earliest experiments in animal calorimetry were those of Lavoisier, who employed the method of direct as well as of indirect calorimetry. Lavoisier showed that animals absorb oxygen with the production of heat. His calorimeter was simply a block of ice hollowed out to form a container large enough for the animal and a supply of air, and covered with another block of ice. The animal was placed in the calorimeter and allowed to remain for a period which had to be brief enough so the air contained in the calorimeter would supply the animal with oxygen and would sufficiently dilute the CO_2 produced. At the end of this period the animal was removed and the water due to the melting of the ice on the inside of the calorimeter was carefully measured. Any heat conducted from the outside melted the ice on the outside only. One kilo of ice on melting absorbs 80 Calories. In some experiments Lavoisier also determined the oxygen absorbed and found that a resting man in air at 26° absorbed 1200 French cubic inches of oxygen per hour. An hour afterward the air was lowered to 12° and he absorbed 1400 cubic inches of oxygen per hour. According to our modern interpretation this increase in absorption of oxygen may be due to muscular exercise in the form of shivering. While digesting a meal the same man absorbed 1850 cubic inches of oxygen per hour, and during exercise, 4000 cubic inches per hour.

In placing a living organism inside a calorimeter it is necessary not only to supply oxygen, but to keep down the CO_2 concentration. This is done by having either a large air space and a short respiration period or by circulating the air and measuring its temperature as it goes in and again as it comes out. In order to keep the temperature inside the calorimeter more or less constant, a cooling coil may be inserted and the heat that is carried away determined by weighing the water and measuring the temperature on intake and exit.

For a large calorimeter a Dewar flask is not obtainable, and the insulation of ordinary insulating material is not to be relied upon. Atwater and Rosa used as insulating material a cork layer. They also employed a means of keeping the temperature of the surroundings the same as that on the inside of the chamber. The chamber was surrounded by six closed-in air spaces, each of which contained an electric heating apparatus and was connected to the interior of the chamber by a thermocouple passing through the wall. When the thermocouple showed that the temperature of the inclosed space was lower than the wall of the chamber adjacent, the heating current was turned on until there was no difference of temperature.

Atwater, Rosa, and Benedict have checked the work by calculating the heat produced from measurement of the respiration (indirect method). At first the oxygen consumed was not determined in the Atwater-Rosa calorimeter. The CO_2 produced was weighed. The subject was either fasted or given carbohydrate as food, and then it was assumed that all of the carbohydrate given was burned if the metabolic period was long. The protein burned, calculated from the urinary nitrogen, was considered body protein. It was not assumed that any loss of glycogen occurred. The body fat that was burned was calculated by the difference in the total CO_2 produced and that calculated as being produced from the burning of protein and carbohydrate. In the later form of instrument the oxygen is weighed, and thus considerable error is eliminated.

An attempt has been made to standardize, as far as possible, the conditions for studies of metabolism in order that results of different experiments may be comparable. For this reason basal metabolism has been defined as the metabolism while the subject is in the postabsorptive condition, and relaxed but awake. Various experimenters have determined the effect of light breakfast, and Barr and DuBois, for instance, report that a breakfast of a slice of bread with 8 grams of butter, 1 cup of caffein-free coffee, with 10 grams of cane-sugar and 66 cc. of milk, does not have an appreciable effect on basal metabolism. Benedict uses coffee and saccharin and 30 g. cream and 25 g. potato chips. Measurements are usually made after fasting from twelve to eighteen hours. A more or less definite period after eating must be set, since during starvation metabolism constantly decreases, with a sharp drop at first and a slow one later.

The nearest approximation to perfect relaxation would naturally be while the subject was asleep, but sleep lowers the metabolism below the basal. Since for so many experiments this condition is not feasible, a period of comparative relaxation has been chosen as the standard—*i. e.*, immediately following at least several hours of comparative rest and following a period of at least half an hour of rest in bed. The temperature of the room must be kept fairly high to prevent shivering. The subject's own temperature must be normal, since it has been shown that an elevation of body temperature of 1° will, on the average, increase the metabolic rate by about 10 per cent. Benedict finds the normal skin temperature 28° to 35°, but on exposure it may go down to 20°. Wood and Hill observed that oxen with lower skin temperature fattened on less food than oxen with higher skin temperature.

In order to have the work on metabolism of great value in clinical procedures it is necessary to have standards for comparison.

This brings us face to face with one of the most difficult problems confronting experimenters in this subject—the establishment of such standards—that is to say, a method of determining an individual's ideal metabolism and the extent to which he may vary from that ideal condition before he is considered abnormal.

The first formulas developed were on the assumption of a definite relation between surface area and radiation of heat, based on Newton's law of cooling,

$$q = k\,\sigma\,t\,(\delta\,T)$$

in which q equals the heat lost during the time t, k is a constant depending on the nature of the surface, σ is the area of the surface, and $\delta\,T$ the degrees temperature above that of the surrounding medium. One of the most serious difficulties in the way of testing this hypothesis has been that of obtaining an accurate measurement of surface area. A number of formulas have been suggested based on the general formula:

$$\sigma = k\,w^{\frac{2}{3}}$$

where σ equals area of body, w equals body weight, and k is a constant. The constants were derived empirically, and the various formulas differed only in the value of k. DuBois and DuBois believe that height as well as weight helps to determine area, and have derived the following formula:

$$\sigma = 71.84\,w^{0.425}\,\mathrm{h}^{0.725}$$

where σ equals area in square centimeters, w is weight in kilograms, and h is height in centimeters.

Other formulas have been worked out eliminating surface area and reading directly in Calories produced. Possibly the two best known are Dreyer's formulas and the formulas of Benedict and Harris. Dreyer's first formula is:

$$\frac{w^n}{\text{Cal. } A^{0.1333}} = k$$

where w equals body weight in grams, Cal. is Calories per twenty-four hours, A is age in years, n is 0.5 (approximately), and k

equals 0.1015 for males and 0.1127 for females. He also worked out a formula for the relation between basal metabolism and height,

$$\frac{\mathrm{h}^n}{\text{Cal. } A^{0.1333}} = k_2$$

where h is body length in centimeters, n is approximately 1.5, k_2 is 1.567 for males and 1.597 for females. Dreyer believes that if an individual is of normal build, the heat determination by these two formulas will give consistent results, but if a person varies widely from the average, an adjustment must be made. Thus, although in the age-weight formula he does not recognize the fundamental importance of surface, he does admit that the form of the individual has an effect on his heat production. The values of the age-weight formula have been tabulated by Stoner.

The formulas of Harris and Benedict are:

$$\text{Cal. } (♂) = 66.4730 + 13.7516\, w + 5.0033\, \mathrm{h} - 6.755\, A$$

$$\text{Cal. } (♀) = 655.0955 + 9.5634\, w + 1.8496\, \mathrm{h} - 4.6756\, A$$

where Cal. (♂) equals total heat produced by males (twenty-four-hour period) and Cal. (♀), by females; w is weight in kilograms, h is height in centimeters, and A is age in years.

Extensive tests have been made of the relative applicability of the formula of DuBois and DuBois and those of Harris and Benedict by figuring the extent of error estimated in individuals whose metabolism had been determined directly. Boothby and Sandiford recalculated the basal metabolism of 8614 subjects, using the two formulas. They found that the rates calculated from the Harris-Benedict formulas are on the average about 4 per cent. lower than those found by the DuBois formula.

The Calories per square meter of body surface vary with age in man, and are at a minimum at birth and a maximum at about two to four years, after which they decrease at first rapidly, then more slowly, until death. The sharp bend in the curve during infancy has been one of the main arguments used against the idea that there is a fundamental relation between surface area and metabolic rate. Nearly all, however, admit that there is a remarkable agreement between them. Lusk believes the correlation to be between calorific output and "active mass" of protoplasm.

That heat production has nothing to do with the law of cooling is evident from the fact that there is no direct relation between the heat production and skin temperature or the external temperature in isothermic (warm-blooded) animals, and the surface law is applicable to some poikilothermic (cold-blooded) animals. The fact that the surface law can be applied is probably due to the composition of organisms of thin membranes which might be called surfaces, since the thickness of these membranes remains more or less constant when the area increases.

This surface law holds only for true basal metabolism of the animal. In some lower organisms, when oxygen is cut off, the heat produced falls to zero, and these organisms may die in about twelve hours or more if oxygen is not readmitted sooner. There is no surface law when muscular activity is included in the metabolism, although the slight muscular activity due to necessary heart beat and respiration is included in what we arbitrarily designate the basal metabolism of man. The muscles are not built up on the membrane plan, although they are, of course, supplied with blood and nutritive substances which have to diffuse through membranes. The surface law is illustrated by the provision for supply of oxygen to the tissues. The trachea brings in the oxygen and the aorta distributes it to the body. The cross-section of the trachea and the cross-section of the aorta are each proportional to the surface of the skin.

It is not possible to go into detail concerning all the applications of study of heat metabolism, but just to indicate some of these. In the first place, the metabolism cannot be accurately calculated from the food consumed unless food that can be completely digested is chosen, such as meats (and milk under certain conditions). In this case the feces consist merely of mucin, bacteria, mineral salts, such as calcium phosphate and water. On eating such foods as string beans the enzymes that digest starch cannot get through the cell walls of the bean, and the starch is undigested, while the sugars are the only carbohydrates absorbed. Vegetable proteins, either on account of their coverings or their physical nature, are not all digested. In the case of proteins of peas only 80 per cent. is digested.

In conclusion, some practical applications may be mentioned. By calculations the amount of carbohydrate burned in diabetes may be determined. The basal metabolism is an aid in diagnosis, since it is high in hyperthyroidism or thyroxin feeding, and is high in hyperpituitism, whereas it is low in hypothyroidism or cretinism or after removal of the thyroid, in hypopituitism, and in some other conditions.

During muscular activity or the absorption of food the metabolism is raised above the basal rate. During absorption of carbohydrates the blood-sugar level is raised and carbohydrates are burned more rapidly. The same may be true of fat.

Protein on absorption exerts a specific dynamic action and raises the metabolic rate. Lusk has studied the specific dynamic action of various amino-acids and found the greatest effect due to glycine and alanine.

According to Plant, the specific dynamic action of protein is decreased in constitutional obesity as distinguished from obesity due to myxedema.

THE CALORIMETRY OF MUSCLE CONTRACTION

The energetics of muscular contraction were at first based on the idea of a heat machine such as the steam engine. Engelmann found that the violin string would contract when the water was heated and would relax again on cooling, but it has been observed that unless the string is stretched or twisted while drying, it will not shorten on absorbing water.

It is well known that a muscle becomes fatigued after long activity in the absence of oxygen, in which case lactic acid accumulates (Fletcher and Hopkins). Harden and Maclean in 1911 found that respiration would not occur in the pressed juice of muscles, that is to say, that the lactic acid is not burned.

The energetics of muscular contraction have recently been advanced considerably by A. V. Hill and by Otto Meyerhof. Hill showed that the heat liberated may be divided into two main parts—action heat and restitution heat. Action heat may be again divided into: first, that which occurs on contraction, and second, that which is liberated gradually on relaxation or continuously during tetanic contractions. Restitution heat is that which is liberated by the oxidation of lactic acid in the presence of oxygen. The restitution heat is produced about one second after a single muscle twitch. The efficiency of the muscle may be 20 per cent., but varies with the load. The energy that might be used in mechanical work will not all be so used unless the proper machine be devised. The most efficient machine would be one that maintained the optimum load all during the contraction which would be a varying load, and in which the relaxation was accomplished without any transfer of energy. Such a machine would be frictionless, but in practice there is always friction inside of the muscle, that is to say, muscle produces heat by its own deformation both in contraction and in relaxation.

Under ideal conditions a large proportion (40 to 50 per cent.) of the energy set free during the contraction may be recovered in mechanical work, but none of the energy represented by the restitution heat is available for the contraction concerned because it occurs after the contraction is over and is due to the burning of lactic acid with R. Q. = 1. It is assumed, however, by Meyerhof that some of this energy is used to restore the muscle to its original state. For instance, lactic acid is produced during the contraction and about 370 gram calories of heat are produced in the formation of a gram of lactic acid from glycogen, whereas the heat of formation of lactic acid from glycogen in a calorimeter is only 230 gram calories per gram. This value of 370 gram calories can be reduced by hanging muscle in alkaline Ringer's solution, so some of the heat is due to the combination of lactic acid with the muscle tissue. Heat is produced by immersing muscle in valerianic acid. This heat is due to combination of H ions with protein, for when 1 gram of lactic acid reacts with concentrated egg-albumin solution, 140 gram calories are produced. The lactic acid produced is neutralized by alkali protein and the pH is not changed more than 0.01 (Ritchie). Meyerhof supposes that the lactic acid causes the shortening, and that it is produced in the fibrils, but the sarcoplasm proteins immediately remove the lactic acid and allow the fibrils to relax. The action heat may then be divided into two parts, the first part during true contraction when lactic acid is produced, and the second part during relaxation when the lactic acid combines with the sarcoplasm.

It was previously supposed that the restitution heat represented the combustion of all the lactic acid to CO_2, but 3836 gram calories would be liberated in the burning of 1 gram of glycogen, whereas the restitution heat equals the action heat, and the total heat is 740 gram calories per gram of lactic acid. Therefore it is assumed by Meyerhof that part of the lactic acid is built back into glucose to be used in later contractions.

Since the total heat produced equals 740 gram calories, and 370 of these appear during the first action phase, the remainder, or 370, would represent the net heat production of the restitution phase, and would represent the algebraic sum of the oxidation of 0.193 gram of lactic acid (exothermic), and the restoration of the remaining 0.807 gram of lactic acid to its original condition (endothermic). These calorific determinations vary so much in the different papers that the reader is referred to the original papers.

According to Embden it is a hexose-diphosphate that is the source of muscular energy. Hence it may be that the lactic acid is transformed back into a hexose-diphosphate, the energy required for this process being derived from the burning of about one-fifth of the lactic acid to CO_2. If glucose is added to the pressed juice the production of lactic acid is not increased, but if hexose-diphosphate is added to the pressed juice the production of lactic acid is increased. In order to determine the phosphoric acid liberated from hexose-diphosphate it is necessary to plunge the muscle immediately after stimulation into liquid air.

In the case of prolonged and heavy muscular exercise lactic acid may pass into the blood and out through the kidneys. The amount of lactic acid produced in a man may be 120 grams according to Hill. The liberation of this amount of acid greatly changes the momentary respiratory quotient in Hill's experiments, but in the total extra metabolism during exercise the R. Q. = 1. Embden observed that the feeding of sodium phosphate to men greatly increased their ability to do muscular work. It has recently been shown by Lusk that the energy required for the restoration of the lactic acid to its original form may be derived from oxidation of fat.

Bethe objects to the assumption that lactic acid causes the contraction, because alkali, alcohol, caffein, chloroform, or heat may produce contraction, but these may cause contraction even of a narcotized muscle or one that is made incapable of stimulation by KCl or cane-sugar solution. Chloroform, alkali, and caffein cause a production of lactic acid.

Bethe maintains that acids or alkalies in causing contraction do not produce as great a tension as in normal tetanus, while chloroform, methyl and amyl alcohol, and heat produce a greater tension than occurring during tetanus. It must be remembered, however, that lactic acid is present in all these cases.

The thermocouples used by Hill to determine the heat produced by the contraction of the sartorius muscle of the frog were very sensitive. Constantan wire of 49 gauge was wound around a thin piece of mica and half of each side coated with shellac. It was then electroplated with silver, the current used being 2 ampere seconds. This deposited silver on the unvarnished surface so that the silver would carry nineteen-twentieths of the current, the junctions of plated and unplated wire then acting as constantan-silver junctions. The wire could be wound so closely as to give thirty junctions per millimeter breadth of the thermocouple.

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CHAPTER IX

COLLOIDS IN ORGANISMS

THE chief colloid in organisms is protein. Some writers have considered protein an ampholyte since it is made of amino-acids, which are ampholytes, but this view is not universally accepted. The general formula for proteins and amino-acids is

$$RCHNH_2COOH$$

in which R represents a carbon chain or a series of them connected by the amino and carboxyl groups. Some of the amino-acids may be nearly neutral, in others the acidic or basic character predominates.

The logarithms of the reciprocals of the dissociation constants of some ampholytes (amino-acids and dipeptids) at 25° are shown in the following table. In aspartic acid the acidic character predominates, and in arginine the basic character predominates.

$-\log K_a$.	Ampholyte.	$-\log K_b$.	pH of iso-electric point.
3.85	Aspartic acid	11.92	3.03
4.39	Glutamic acid	.....	....
4.79	m-Aminobenzoic acid	10.91	3.79
4.92	p-Aminobenzoic acid	11.63	4.20
7.74	Glycylglycine	10.70	5.52
7.74	Alanylglycine	10.70	5.52
7.82	Leucylglycine	10.52	5.66
8.16	Taurine	.....	....
8.28	Asparagine	11.74	5.27
8.40	Tyrosine	11.58	5.41
8.66	Phenylalanine	11.89	5.35
8.66	Histidine	8.24	7.21
9.70	Alanine	11.28	6.72
9.74	Glycine	11.55	6.58
9.74	Leucine	11.49	6.54
11.00	Lysine	7.00	9.00
13.96	Arginine	7.00	10.48

The double nature of these substances is shown by the following: If HCl is added to glycine, the hydrochloride is formed. The process may be pictured as follows: the glycine no longer dissociates H ions, owing to the large number introduced in the HCl, and the H ions already dissociated recombine with the glycine. The amino group of the glycine binds H ions or dissociates OH ions, so that glycine$^+$ is formed, and if an electric current is passed through the solution the glycine will go to the cathode. When KOH is added to glycine solution K-glycinate is formed, and the details of the process may be pictured similar to the above. If an electric current is passed the glycine$^-$ will go to the anode.

At a certain reaction of the solution either the amino-acid will not migrate in an electric field, or half will go toward the cathode and half toward the anode. The reaction at which this occurs is called the iso-electric point for the amino-acid. At the iso-electric point there may be one of two conditions present. Either there will be an equal number of positively and negatively charged ions, or there may be a number of neutral molecules accompanied by equal numbers of positive and negative ions. Pauli has made the following generalization: If we represent by K_a the dissociation constant of the carboxyl group of the amino-acid and K_b the dissociation constant of the amino group, then when $K_a = K_b$ the iso-electric point will be reached in a neutral solution. If they do not equal each other, the amino-acid will not be iso-electric in a neutral solution, but will be iso-electric at some other hydrogen ion concentration. If the product of K_a and K_b is equal to 10^{-12} or more, there are no neutral molecules, but there are equal numbers (at the iso-electric point) of positively and negatively charged ions. If $K_a = K_b = 10^{-7}$ (their product $= 10^{-14}$), then there are a small number of neutral molecules at the iso-electric point, which is the point of neutrality, accompanied by equal numbers of positively and negatively charged ions. If $K_a = K_b = 10^{-8}$ (their product $= 10^{-16}$), then there are a large number of neutral molecules, other conditions being the same. If $K_a = K_b = 10^{-11}$ (their product $= 10^{-22}$), then all of the molecules are neutral at the point of neutrality of water and there are no positively nor negatively charged ions. Furthermore, the hydrogen ion concentration may be varied between 10^{-6} and 10^{-8} without the appearance of an appreciable number of ions. In fact, it has to reach 10^{-3} in order to obtain 50 per cent. of positively charged ions or 10^{-11} to obtain 50 per cent. of negatively charged ions. If K_a is not equal to K_b the iso-electric point is not the point of neutrality of water, but the product relations are the same—*i. e.*, in order to obtain the broad zone with all the molecules in neutral condition it is necessary to have $K_a \times K_b = 10^{-22}$ or less.

Since proteins are formed of amino-acids, the method of dissociation may be similar to that of amino-acids, but according to Gortner and Hoffman the combination of protein with acids and bases is chiefly by adsorption outside the *p*H range of 2.5–10.5.

The determination of the iso-electric point was first made by electrophoresis (cataphoresis)—*i. e.*, the protein solution was placed in a U-tube through which an electric current flowed. It was observed that the protein migrated either to the anode or to the cathode. The hydrogen ion concentration was changed until the protein ceased to migrate. This was the iso-electric point. From what has been said before it seems that it may either migrate in both directions simultaneously or it may be possible to change the hydrogen ion concentration over a considerable range without its migrating in either direction. At the same time it will diffuse in both directions, although it diffuses slowly. Then, too, if any convection currents are present it will be carried more rapidly. Therefore, the determination of the iso-electric point is difficult.

Another method of determining the iso-electric point is to change the hydrogen ion concentration and to apply various tests other than electrophoresis to determine the maximum number of neutral particles. Although the particles of protein that have lost their charge do not ordinarily precipitate, they may be made to precipitate by various means after losing their electric charge. They also show lowered osmotic pressure. In the case of polyvalent substances like these, the salts may dissociate and lead to more than double the osmotic pressure. Hence, the point of minimum osmotic pressure may be considered the iso-electric point. If an iso-electric zone exists, there will be a zone of low osmotic pressure.

A fourth method depends on the fact that the iso-electric point is the point of minimum viscosity.

A fifth method of determining the iso-electric point is to find the H^+ concentration that remains unaltered on addition of various amounts of the protein. Of course, this protein should be at the iso-electric point when added.

It has been shown that proteins differ in electric charge not only on change of hydrogen ion concentration but also on change of other ions. Therefore the protein does not behave in exactly the same way in hydrochloric acid as it does in acetic acid of the same hydrogen ion concentration.

The iso-electric points or zones of many animal proteins are on the acid side of neutrality, and those of the vegetable proteins vary rather widely. The following table gives the *p*H at the iso-electric point:

Protein.	*p*H at iso-electric point.
Egg albumin	4.8
Serum albumin	4.7
Serum globulin	5.4
Casein	4.7
Gliadin	9.3
Edestin	7
Oxyhemoglobin	6.74
Pancreas nucleoprotein (trypsin)	3.52
From typhus bacilli	4.4
From paratyphus bacilli	4
Fibrinogen	5

Ordinary gelatine is iso-electric at *p*H 4.7, but on the addition of NaCl the iso-electric point may be displaced to *p*H 3.3.

Bechhold (1908) forced colloid sols through ultrafilters of different sized pores, and in this way classified the sols according to size of particles (or filtratability). The order is as follows, beginning with sols of larger particles:

(Colloidal iron)
Casein
(Colloidal gold and silver)
Gelatine
Hemoglobin
Serum albumin
Diphtheria toxin
Protalbumoses
Lysalbinic acid
Dutero-albumose A
Dutero-albumose B
Litmus
Dextrin

The effectiveness of ions in precipitating hydrophile colloids varies with the charge on the colloid. The Hofmeister series of anions is

$$CNS, I, NO_3, Cl, CH_3COO, SO_4, \text{tartrate}, \text{citrate}$$

The order in precipitating acid albumin is

$$CNS < I < Br < NO_3 < Cl < \text{acetate} < \text{citrate} < SO_4$$

The order of cations in precipitating fibrinogen is

$$Rb < Li < Na < K < Cs$$

and

$$Ba > Sr > Ca > Mg$$

With some negative hydrophile colloids, however, the order is

$$Li < Na < K < Rb < Cs$$

The swelling of gels is influenced by the Hofmeister series. Some sulphates and tartrates cause gelatine to shrink. Bromides and nitrates cause it to swell. Their effect on gelation of sols is:

$$SCN < Br, < NO_3 < Cl < CH_3COO < \text{citrate} < \text{tartrate} < SO_4$$

Glycerol, glucose, and cane-sugar shrink and increase the viscosity of gelatine and starch gels, and urea swells and decreases the viscosity. The Hofmeister series for negative sols is reversed for positive sols and becomes irregular near the iso-electric point. It is claimed by some investigators that the *p*H is the only factor and the salts used in showing the Hofmeister series act as buffers, changing and stabilizing the *p*H. Gortner, however, has shown that the pH is not the only factor and that the anions of acids have an influence.

HYDRATION AND SWELLING OF PROTEINS AND COLLOIDAL CARBOHYDRATES

It has been shown, especially by MacDougal, that carbohydrates swell most in water, and both acids and bases as well as salts reduce the swelling.

Proteins swell least at the iso-electric point, and since most animal proteins have an iso-electric point on the acid side of neutrality and since the blood and body fluids and even cell juices are on the alkaline side of the iso-electric point, the addition of acid first reduces the swelling until the iso-electric point is reached. Both acids and alkalies when added to iso-electric protein increase the swelling up to a certain concentration of H and OH ions. The effects of higher concentrations are too complicated for us to consider in the space that is at our disposal.

It was assumed by Procter and Wilson that the swelling of proteins is due to the osmotic pressure of the accompanying ion. They did not attribute any osmotic pressure to the protein ion; in fact, the protein was in the form of a gel and not free to diffuse, and therefore they assumed that it could exert no osmotic pressure of itself. If we view osmotic pressure quantitatively as stated in Raoult's Law, then the osmotic pressure of the protein would be proportional to its effect in lowering the vapor tension of water, and it might do this whether it is free to diffuse or not. In other words, if the protein cannot go to the water, the water can come to the protein. Procter and Wilson, however, assumed all of the osmotic pressure to be due to the accompanying ion, and they calculated the osmotic pressure from Donnan's equation. They used this in a study of the swelling of gelatin and also in the swelling of hides, particularly in the tanning process. Since the swelling was proportional to the osmotic pressure, the data of Sörensen on the osmotic pressure of pure egg-albumin may be considered in relation to the theory of swelling.

Early work on proteins was done with very impure samples; perhaps the first work on highly purified samples was that of Sörensen and his collaborators, on egg-albumin. By a large number of recrystallizations they obtained crystals of pure egg-albumin, or what we might call egg-albumin sulphate, as two molecules of the albumin were bound with three molecules of sulphuric acid and 830 water molecules (molecular weight 34,000). They showed that egg-albumin solution of given composition invariably exerted the same osmotic pressure. Ammonium sulphate affected the osmotic pressure by lowering it, especially when the ammonium sulphate concentration was fairly large, probably by causing an aggregation of the albumin molecules. The osmotic pressure was lowest at $p\text{H} = 4.25$ in the presence of 4 per cent. $(NH_4)_2SO_4$. On increasing the hydrogen ion concentration the pressure increased very slowly, but on lowering the hydrogen ion concentration below $p\text{H} = 4.4$ there was a rapid increase in pressure. They found that egg-albumin combined least with acids or bases at $p\text{H} = 4.8$, which would indicate that this is the iso-electric point rather than $p\text{H} = 4.25$.

W. F. Hoffman observed that the values of the logarithm of the equivalent of HCl bound per gram of casein or durumin plotted against the pH of the mixture fell almost on the same straight line. This might indicate that not all of the amino and imino groups were used up, but he calculated that they would be if the binding were salt formation, and that, therefore, the binding in high acidity is a case of adsorption. These proteins bound more H_3PO_4 than HCl at the same pH. He found that except in low concentrations of acid or base the binding is the same per gram of protein irrespective of the chemical nature of the protein. He considered this further proof that the binding is adsorption.

The swelling of a protein at its iso-electric point might, therefore, be due to the accompanying ions, which would be present in equal numbers, positive and negative, or it may not be. It may be due to capillarity. Derby found that rubber swells by capillarity.

The swelling of proteins in water is sometimes spoken of as hydration. It is also stated that protein sols are hydrated. It was shown, however, by Hofmeister and others that if gelatin swells in a salt solution, the concentration of these salts in the swollen gelatin is practically the same as that in the surrounding solution, as though water went in by capillarity. Since it is maintained that ions are hydrated, if we assume that the water in the swollen gelatin is all hydrate water we must suppose that both protein and inorganic ions can share the same hydrate water. Neuhausen attempted to measure the hydration of the serum proteins by determining the vapor tension of serum at body temperature. He did not find evidence for any of the water being combined with protein. Newton and Gortner found that the proteins in winter wheat sap bound a certain proportion of the water so that it did not take part in the solution of cane-sugar.

It has been assumed that the viscosity of sols is a measure of hydration. Sharp and Gortner have used viscosity as a measure of the hydration capacity of the proteins of wheat flour. Their work is of great interest from the standpoint of the theory of loaf-volume in baking. Gortner and Newton have used as an index of the hydration capacity of the proteins of hardy winter wheat the force required to press out juice from 100 grams of the green blades of wheat after successive freezing and thawing. With a pressure that will press out 60 cc. of water from wheat that is not hardy only about 1 cc. could be pressed out from the hardy strains.

It was shown by Starling that the blood volume is dependent upon the osmotic pressure of the proteins. When the blood passes through a glomerulus of the kidney the force of blood-pressure presses out the substances to which the wall of the glomerulus is permeable. Since this wall is not permeable to protein the filtration will cease when the osmotic pressure of the proteins equals the blood-pressure in the glomerulus. The corpuscles shrink in size because of increase in CO_2 while passing through the capillaries. The water they lose in the glomerular capillaries may filter out.

F. H. Scott has shown that similar relations hold for equilibrium in regard to water between the blood-corpuscles and the blood and also between the blood and the tissues. He has shown that the blood-vessels in the tissues, particularly in the liver, are slightly permeable to protein. Where rapid changes take place they may be considered impermeable. He has found that when water is added to blood, all of the water passes into the corpuscles—at least insofar as the analyses show. Since the greater amount of the protein is in the corpuscles it is to be expected that by far the greater amount, but not all, of the water will enter them. The non-diffusible substances in the blood maintain the blood volume, and therefore salt solution injected intravenously after hemorrhage rapidly passes out of the blood. For this reason a large amount of work has been done on injection of gum acacia to restore the blood-volume. Although the gum acacia does not remain permanently in the blood-vessels, it remains there longer than salt solution, and since the vessels are slightly permeable to protein, and since protein comes in also by the thoracic duct, the gum acacia is gradually replaced by protein even before the body has time to regenerate the blood-proteins lost by hemorrhage.

As living cells contain colloidal proteins, carbohydrates, and lipins, and the swelling of the cell may be a function of all three, MacDougal has studied the swelling of plates of agar and gelatin, agar and bean protein, agar, gelatin and soap, and other combinations, and the effect of various electrolytes and non-electrolytes on the swelling. Besides studying the equilibrium he has made very accurate determinations of the rate of swelling. According to Tieback (1911) a mixture of gelatine and gum arabic behaves like a globulin, particularly like casein, as regards swelling. Beijerinck (1910) claims that a hot 10 per cent. gelatine solution and hot 2 per cent. agar or 10 per cent. soluble starch, do not mix, but form an emulsion. Dried seaweed has been observed to take up water against a pressure of 40 atmospheres, and soluble starch will take up water against a pressure of 2500 atmospheres (Rodewald). The swelling pressure of gelatins of different water contents is given by Posnjac (1912) as follows:

Pressure in cm. Hg	337	303	240	156	82.4	38.3
Grams H_2O per 100 gm. gelatine	92	110	128	146	206	256

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CHAPTER X

HYDROGEN IONS IN BIOLOGY

HYDROGEN-ION CONCENTRATION AND ENZYMES

Each enzyme has a particular *p*H at which the action is most rapid. The following table gives values for a number of enzymes:

Enzyme.	Optimum *p*H.	Alk. inhib.
Autolyzing liver	5	9
Proteolysis of fibrin by trypsin	8	
Proteolysis of gelatin by trypsin	9.7	
Proteolysis of peptone by trypsin	7.7	
Proteolysis of casein by trypsin	6	
Proteolysis of peptone by trypsin	8.3	
Pepsin	1.5–2	
Pepsin (plastein foundation)	1	
Bact. protease	7.2	
Malt protease	4.5	
Erepsin	7.8	
Rennin	5.7	
Pencillium amylase	3	8
Pancreatic amylase	6	
Ptyalin, amylase	6.7	
Invertase	4.5	
Glycolase of blood	7.52	
Maltase	6.6 (3 at 35°, 7.2 at 47°)	
Maltase (splitting of a-methylglucoside)	6.2	
Cellase	6	
Inulase	3	
Laccase	7	
Combination of urease-urea	8.7	
Dissociation of urease-urea	7	
Gastric lipase	6.3–7.0	
Pancreatic lipase	8	
Castor bean lipase	3	
Esterase of blood	7.8–8.5	
Catalase of blood	7	
Catalase of liver	7	

HYDROGEN-ION CONCENTRATION OF THE ALIMENTARY TRACT

The saliva is approximately neutral in reaction. It is asserted by Andresen that the mucous and serous parts of the saliva have different hydrogen ion concentrations and that the greater proportion of the buffer is in the serous part. The buffer is composed chiefly of bicarbonates, though phosphates and proteins are present. The bicarbonate (alkaline reserve) may be titrated by adding an excess of standard acid, blowing out the CO_2 with CO_2-free air, and titrating back with standard CO_2-free alkali. It was shown by Robb and his collaborators that the alkaline reserve on a normal diet giving an alkaline ash is about 0.008 *N*. On a scurvy diet which not only lacked the antiscorbutic vitamin but also had an acid ash, it fell to 0.004 in about a week. Certain substances of sharp (acid) taste in the mouth stimulate the salivary glands and saliva of higher alkaline reserve is secreted. Thus in one experiment the alkaline reserve was found to be 0.007; then lemon juice was taken into the mouth, and after ten minutes the alkaline reserve had risen to about 0.014 *N*. It is necessarily true that if such a solution is exposed to the air so that CO_2 can escape, the *p*H will increase, and this is actually shown to take place by experiment. Even air reaching the saliva in the mouth cavity increases the *p*H, and if air is blown through the saliva, the *p*H is still further increased. Therefore, the finding of an alkaline saliva in the mouth cavity does not mean that it was alkaline when secreted.

Not only is it impossible that the saliva should dissolve the calcium phosphate of the enamel or exposed dentine, but calcium phosphate is even precipitated from the saliva on to the teeth. It may, however, be possible that down under bacterial plaques or masses of precipitate or colloid aggregates, and in the presence of carbohydrate, bacteria may produce sufficient acid to etch the enamel. The saliva contains a very slight trace of glucose and also a glycoprotein (mucin). Carbohydrates of the food probably do not remain on the teeth very long, starch being hydrolyzed by the saliva and washed away.

Stomach.—Hydrochloric acid was discovered in the gastric juice by Prout in 1824. It had been previously considered that the acid in the stomach was due to fermentation; in fact, that idea influenced clinical observations for a long time, and various methods were used to determine the amount of fermentation in the stomach. Prout's fundamental discovery cleared up the whole question of the acidity of the stomach for those who could interpret his findings, but there has been a great deal of discussion and misunderstanding concerning this question. It was shown by Menten and others that the human gastric juice is almost pure 0.1 N HCl solution. No acid is produced in the pyloric glands.

It was supposed that the border cells of the fundus glands secrete the acid. Harvey and Bensley showed that there is no HCl in the cells themselves, although Collip supposed that there is HCl on the cell border. Since HCl is not secreted as such, and since chlorides are strong electrolytes, it follows that the hydrogen ions and chlorine ions are secreted separately. For the mechanism whereby this may take place the reader is referred to the section on Anomalous (Negative) Osmose, Chapter XII. To summarize the process here it seems possible that NaCl diffuses through a membrane of relatively large pores from the blood into the gastric lumen, and since Cl^- diffuses more rapidly than Na^+, this makes the lumen electronegative. At some other region of the stomach wall the pores are smaller and NaCl cannot get through, but hydrogen ions being very small can enter and are drawn in by the negative charge. In other words, the secretion of HCl is a continuous process, the chlorine ions coming in through one region of large pores and the hydrogen ions through the general surface against a concentration gradient. This hypothesis would necessitate that some sodium ions also enter, but not as many as the chlorine ions, and it is true that gastric juice contains sodium ions. This hypothesis has not been worked out quantitatively, however, in order to show that it is possible to obtain a 0.1 N solution of hydrochloric acid in this way. The experiments of Bethe and his collaborators have demonstrated that the reaction of a solution separated from another solution by a membrane may be altered by the passage of an electric current through the membrane. The electric currents produced by secreting glands have been measured very often. The hypothesis then has been tested qualitatively.

It was shown by Boldyreff that regurgitation of pancreatic juice into the stomach might occur. The gastric juice does not remain 0.1 N HCl, but is partly neutralized by the bicarbonate of the saliva and the pancreatic juice as well as by the mucin and food proteins. It can be obtained pure in dogs by means of the Pavloff pouch, and in some human beings who possess gastric fistulæ. Ordinarily a somewhat diluted gastric juice is obtained after taking the Ewald test-meal which consists of 35 grams of toast and 250 cc. of tea. The concentration of hydrochloric acid depends on the rate of secretion and the rate of combination and dilution. It was shown by McClendon that owing to the regulatory motor mechanism there is a maximum hydrogen ion concentration of the stomach contents in each individual, but that this maximum may be slightly different in different individuals. It varied between $p\text{H} = 1$ and $p\text{H} = 2.5$. If a large meal is taken the maximum hydrogen ion concentration requires more time to be attained than after a small meal. The Ewald test-meal has the advantage that it is very small. If the pylorus is tied off, acid is continually secreted until the acidity may rise almost to equal that of pure gastric juice. The pylorus may be closed spasmodically in certain diseases. This gives rise to what is known as hyperacidity. In no case is gastric juice of an abnormally high hydrochloric acid content secreted, but sometimes juice may be very scanty or perhaps of low acid content, both conditions being designated hypoacidity or achylia.

According to Carlson, hypoacidity may exist in the following conditions: (1) Achylia simplex, (2) cancer (appears late in case of human cancer and not at all in case of experimental rat tumors), (3) anemia, (4) infantile anorexia and atrophy, (5) gall-bladder disease, (6) chronic colitis, (7) hypothyroidism, (8) heart disease, (9) eclampsia, (10) pellagra, (11) beriberi, (12) dilatation of the stomach—hypoacidity due to regurgitation—and (13) fevers. If the diet is free from chlorides, gastric secretion is completely inhibited, as the body's store of chlorides is sufficiently depleted. Frouin observed that a chloride-free diet for eight days completely inhibited gastric secretion in dogs. According to Wiener, a high chlorine content (0.34 to 0.58 per cent.) with low acidity differentiates malignant disease from simple achylia. Ylppö found that fever may decrease gastric acidity in infants.

The hydrochloric acid of the stomach contents may be titrated, using an indicator that changes color at a relatively high hydrogen-ion concentration. Methyl violet, which goes through a series of color changes, may be used. There are a number of old-fashioned indicators which would not be selected nowadays. Perhaps the most convenient indicator is brom-phenol-blue. A measured quantity of the gastric contents is colored pale yellow with this indicator, and standard NaOH solution is run in until the color changes. The exact shade of the color is difficult to describe because it depends upon the color of the source of light. It is bluish in daylight and reddish in artificial light.

Various methods have been devised for determining the so-called combined hydrochloric acid. If hydrochloric acid is added to food the proteins combine with some of it. Ege advocates the titration of the acidity to the reaction of the test-meal, but he is in error in supposing that this determines the total acid secreted, because some of it is neutralized by the saliva, and duodenal regurgitation may take place. Unless the pylorus and cardia are tied off, it is impossible to determine by titration the total amount of acid secreted. Therefore it seems wasteful of time to determine what is called the total acidity when it is impossible to interpret the results in chemical terms.

The digestion in the stomach depends on the hydrogen ion concentration and not on the total acid secreted. It is therefore instructive to determine the hydrogen-ion concentration. This may be very easily determined as indicated above (Chapter IV) by the use of a Duboscq colorimeter and quinaldine red.

The acidity of the infant's stomach contents is variable. According to Mariott and Davidson, at the height of digestion the *p*H averages 3.75.

The acidity of the stomach kills some bacteria. It is pointed out by Demuth that at a *p*H of 4.5 Bacillus coli is still found in the stomach of healthy children, but according to Mariott at a pH of 4 there is almost complete inhibition of the colon typhoid group.

The Duodenum.—Van Helmont in 1648 observed that the acid chyle on passing into the duodenum loses its acid taste and acquires a salty taste. This is due to the neutralization of hydrochloric acid by means of sodium bicarbonate secreted by the pancreas and intestinal glands. It seems possible that a thin layer of fluid on the inner surface of the intestine may be alkaline, but the contents of the duodenum are usually acid, though not

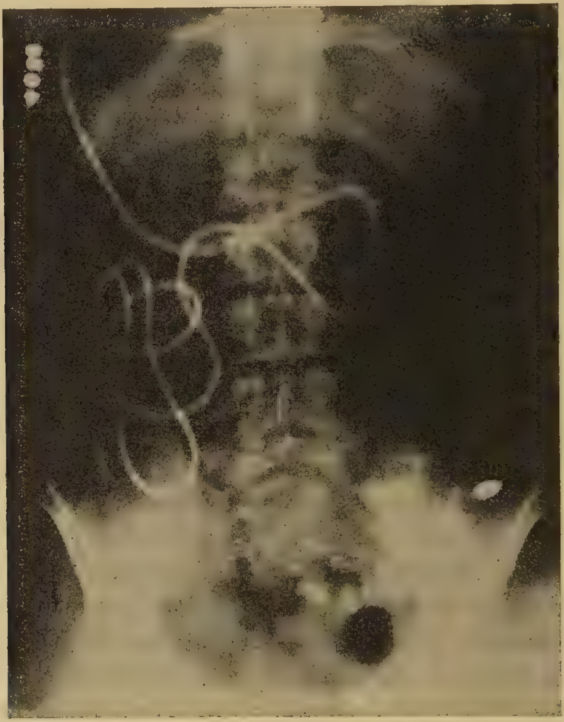

Fig. 18.—*x*-Ray plate showing rubber tube passed 7 feet from the mouth down into the small intestine of a man. Above the hip bone on the right-hand side of the figure (left-hand side of the subject) the white oval represents a 6-g. iron weight that was tied on by catgut to hasten the descent, but is now released by the digestion of the catgut.

sufficiently so to taste acid. It was shown by Long and Fenger that the duodenum may vary from very acid to slightly alkaline (pH 2.27 – 7.8). It has been shown by means of x-rays that the stomach contents spurt out into the duodenum periodically, therefore we cannot expect a uniform reaction. Hume, Denis, Silverman and Irwin obtained values of 5.9 to 8.23.

Ileum and Jejunum.—In 1891 Macfadyen and his collaborators studied for six months the outflow from a fistula in the lower part of the ileum of a patient. They found the reaction of the ileum and cecum always slightly acid, and more acid the greater the sugar content. McClendon and his collaborators showed by means of tubes passed 2 meters from the mouth into the ileum that the further down they passed, the less the acidity (Fig. 18). The pH of the lower part of the duodenum varied from 4.5 to 5.1. In the ileum it varied from 5.9 to 6.5. Okeda observed pH values ranging from 4.8 to 7.9.

The pH of the duodenum of the infant was observed by McClendon and his collaborators to be very variable, the usual value being about 3.

In the absorption of fats intestinal juice may play an important rôle. Fats are usually considered as being absorbed in the form of glycerol and fatty acids, the latter in solution in bile or as soap. Soaps cannot exist in the reaction of the normal human intestine during digestion. It is possible that they may be formed in a thin layer next to the intestinal wall.

The small intestine of the herbivora is very long, and the acidity of the contents decreases from the stomach on down, and usually turns alkaline possibly because of ammonia formation. It is acid, however, in the suckling of herbivora. It was shown by McClendon and his collaborators that a high sugar diet changed the reaction of the intestinal contents of adult rabbits from alkaline to acid and increased the acidity of the intestine of carnivora.

There is no hydrochloric acid present in the ileum or jejunum. The number of weak acids may be very large. It was shown by McClendon and Sharp that the ordinary foods are acid, milk being the only one that approaches neutrality. The hydrolysate of the animal proteins is acid due to the amino-acids. Various organic acids may be present in the foods and lactic acid, and perhaps formic and acetic acids may be formed in the intestine.

Large Intestine.—Although the contents of the cecum may be slightly acid, the acidity is probably reduced on the way along the large intestine because of ammonia formation, so that the adult feces may be slightly alkaline. According to Robinson, the *p*H of the feces is from 7 to 7.5. In diarrhea they may become acid. The *p*H of the feces of breast-fed infants who are growing rapidly varies from 5 to 6 according to Hainiss. He attributes the health of the infant to the reaction favorable for the growth of Bacillus bifidus.

BACTERIA AND THEIR *p*H RANGE

Organism.	Acid inh. (*p*H).	Alk. inh. (*p*H).	Opt. *p*H.	Final *p*H.
YEASTS:				
Bakers' yeast			3–6	
Brewers' yeast			4–6	
Torula yeast			2.5–6	
FUNGUS:				
Imochi fungus	3.1			
Sclerotinia apothecia	1.4	7–9	2.5	
BACTERIA:				
B. diphtheriæ	5.8–8	8.3	7.5	
B. tuberculosis horse	6	7.6	7	
human				4.4–7.4
B. typhosus	5-6.2	7.6–8.6	6–7	
B. coli	4.7–4.4	7.8	7–6.5	5
B. paratyphosus A	4.5	7.8	6.7	
B. paratyphosus B	4.5	8.0	6.8	
B. suipestifer	5.0	8.2	7.3	
B. pyocyaneus	5.6	8.0	6.9	
B. proteus vulgaris	4.4	8.4	6.5	
B. prodigiosus	5	8	6.5	
B. sp. choleræ	6.4	7.9	7.2	
B. cinnavarens	5	7.8	6.5	
Pneumococcus	7	8.3	7.8	5–5.6
Strep. mastitis				4.5
Strep. liquefaciens	5.5	8	6.6	
Strep. hemolyticus				4.8–5.4
Staphylococcus	2–5.6	8.1–10	5.7–7.4	
Gonococcus	6	7.8	7–7.6	3.7
B. subtilis				
B. anthracis				

Organism.	Acid inh. (*p*H).	Alk. inh. (*p*H).	Opt. *p*H.	Final *p*H.
B. anthracoides				
B. pfeiffer	6.2	7.6	7	
B. pestis	5.6	7.5	6.8	
B. sporogenes B. histolyticus B. canadiensis B. putrificiens B. perfringens	5.8	8.5	6.8	
B. tetani	5.5	8.3	7.3	
B. bifidus	2.3–4.2			
B. macreans	5		6.8	
B. casei	3.1–3.4		7.1	3
Strep. lactis	3.1–3.4		7.9	4
Strep. lactis from pressed yeast	4.8–4.9			4.4

It has been stated that bacteria may adapt themselves to changes of hydrogen-ion concentration, but the adaptation seems to be very slight. For instance, with the diphtheria bacillus *p*H 7 has been given as the optimum, but strains with optima from 7.2 to 7.6 are found, and at least one strain has been able to develop in a zone from 5.8 (acid inhibition) to 8.4 (alkaline inhibition) at 37°. After growing for some time in a more acid medium than the optimum, the region of most rapid growth was shoved slightly to the acid side.

The *p*H may affect slightly the metabolism of the bacillus, as was shown in some experiments with Bacillus typhosus. In certain other experiments the bacilli themselves produced the change in *p*H which was started at 7.4 with 1 per cent. dextrose. Strains giving the more acid final reaction used less dextrose than the others. Also, in cultures at or near the optimum reaction, the bacilli produce more CO_2 than they do far away.

The effect of the H-ion concentration on the life of the bacillus varies also with temperature, and it has been found in processing canned foods that the more acid the food the lower the temperature necessary for sterilization, proving, of course, that the food is more acid than the optimum for the bacillus. Since all foods are on the acid side of neutrality, it is easy to get them more acid than the optimum of different types of bacilli.

Sterilization with sublimate is favored by acidity. For instance, sterilization by sublimate at a concentration of 1 to 100,000 to 600,000 goes on very well at a *p*H of 5 to 6.6, but not nearly so well at a *p*H of 7.8 to 10.1. It is possible that the alkaline solution causes a hydrolysis of the sublimate.

If the bacilli die they may or may not dissolve. The dissolution of the pneumococcus is most marked at a *p*H range of 5 to 7. This dissolution is probably due to an enzyme in the bacilli themselves that has its optimum range at this *p*H. Now it is found, for instance, that the hemolysis of sheep corpuscles is inhibited by high acid or alkali, but occurs at the rather wide *p*H range of 5.45 to 9.3.

The specific precipitation of a protein (egg-albumin for instance) by immune rabbit serum occurs between *p*H of 4.5 to 9.5; outside of this range the precipitate either does not form, or if it does form it will redissolve. Bacteria are agglutinated by immune serum, and the medium in which the reaction occurs increases in alkalinity. This change in alkalinity may affect the relations between the bacteria and the antibody. For instance, the washing off of the antibody from bacteria is affected by the *p*H. In the case of Bacillus typhosus removal is more complete at a *p*H of 3 than at a *p*H of 7.

The *p*H affects the toxins produced by bacilli; for instance, the diphtheria bacillus does not seem to produce any toxin at a *p*H greater than 8.6.

The activity of the toxin of the diphtheria bacillus is less when the *p*H is below 6.8. Alkalinity and acidity are both unfavorable to the preservation of the toxin.

To sum up the main points: The effect of *p*H on bacteria varies, and the optimum for the growth of a species is at a very definite and often very narrow range. One significance of this for the life of an ordinary person is that in the intestine where there is a mixed culture the dominance is affected by the *p*H. Since the dominance is also affected by the substrate or food substances, such as sugars, in solution it is sometimes difficult to dissociate these two effects. For instance, the main groups of bacteria are the fermentative and the putrefactive groups. The former are always found in predominance in the more acid media, and the latter in the more alkaline. By feeding herbivorous animals and also carnivorous animals large amounts of lactose it was found by McClendon and collaborators that the *p*H of the intestine was decreased (acidity increased).

Numerous investigators have found that under those conditions the fermentative bacteria, such as Bacillus bifidus and B. acidophilus, are in predominance. With a higher *p*H the putrefactive bacteria may possibly be in predominance. Thus it seems that the bacterial contents of the intestines may change as the result of a change in *p*H which the bacteria themselves have brought about—in this specific case by the fermentation of lactose.

HYDROGEN-ION CONCENTRATION OF SOILS

Soils are the home of protozoa, bacilli, fungi, and the roots of the higher plants. It is chiefly in regard to the last that the *p*H of soils has been studied. Many plants grow in either acid or alkaline soils. Certain higher plants, such as the grasses, can exist in acid soils, whereas many of the plants, such as alfalfa, are favored by neutral or slightly alkaline ones.

Plants requiring a high *p*H (neutral or alkaline soil) have a high lime requirement, and vice versa. Of the legumes, sweet clover has the highest lime requirement and the blue lupine the lowest. Of the cereals, barley has the highest lime requirement, corn and spring wheat medium, and the rest are low. Grasses are medium or low. Cabbage, onion, lettuce, cauliflower, spinach, sugar-beet, celery, tobacco, and mulberry trees have very high lime requirements. Cranberries, blueberries, and pine trees have very low lime requirements.

In the black peaty soils the *p*H may be around 3.5 to 6.5, and in the calcareous soils the *p*H may be around 6.5 to 9. High acidity may be due partly to the oxidation of sulphur derived from pyrites present. The alkalinity of well-drained soil is usually due to $CaCO_3$ or $Ca(HCO_3)_2$, but many of the western soils in this country that are not well drained, that is, in desert regions where the water merely evaporates from the surface, have an alkalinity due chiefly to Na_2CO_3 and $MgCO_3$. The bases (carbonates) increase with increasing depth, the organic matter decreases. Hence, in most soils there may be greater acidity on the surface. In some very wet peat the acidity may decrease toward the surface because of loss of CO_2 at the surface. Arrhenius found that the Egyptian soils are all on the alkaline side of neutrality, *p*H 7 to 11, those yielding good crops having a *p*H of 7.5 to 8.5. The bad alkali soils producing no crops have a *p*H greater than 9. It seems possible that these values have not been corrected for the salt effect on the indicator.

Seedlings of wheat, corn, and soy beans are found not to grow in *p*H less than 3. Maximum growth of wheat seedlings occurs at a *p*H of 6.5; of corn, at a *p*H of 5. A *p*H greater than 6 may give chlorosis due to the insolubility of iron. This condition could be prevented by the addition of acid to neutralize the solution.

Since foods are acid, we should expect them to affect the *p*H of the medium. Similarly, if seeds, particularly the seedlings of grain, are placed in distilled water, the acidity of the water is markedly increased. The acidity may be higher in contact with rootlets than elsewhere, and thus effect absorption of iron from alkaline soils.

Many colored plants except the green plants possess sap that, when squeezed out, can be used as an acid-alkali indicator; but a change in the color of aërial parts of plants does not always mean the same change on the inside that occurs at the roots. In the case of hydrangeas addition of substances that will produce acidity to soil gives a distinctly blue color, as, for instance, ammonium alum or iron sulphate. Where the ammonia is used up and alumina precipitated, the sulphuric acid gives acidity to the soil. The alum, however, may be toxic.

The buffer value of the soil as well as its *p*H is of considerable importance. Humus increases the buffer value because it contains acid substances. Probably it acts as a colloid or protective colloid or as a peptizing agent, and increases the colloid dispersion of the soil. The soils of the rice fields in Java did not show a relation of fertility to the *p*H values, but the greater the buffer action, the greater the fertility. Since acids are produced by the plants themselves the buffer action becomes of importance. Lime is added to increase the pH of soils. Certain acid soils of Oregon respond to lime treatment, others do not. Those that do respond to lime treatment show an increased production of nitrate through the action of bacteria.

The acidity of the soil may reach such a value as to have an inhibitory effect on certain pathologic organisms, for instance, the organism of wheat scab, whose growth is inhibited by pH of 6 or less, and potato scab, whose growth is inhibited by a pH of 4.5 to 5.1.

Other organisms besides bacteria and higher plants are affected by soil acidity. At pH of 4.8 there are very few Hyatinias (snails), whereas at pH of 7 they are numerous; at pH of 8 certain species are killed out, and others, such as Helicella caperata, are more abundant. Upland peat has a pH of 4.6, and rough pastures, a pH of 5.4, in some French experiments. Now the liming of these soils would produce a reaction more favorable to the snails. The interest from a medical standpoint is that these snails are the hosts of one generation of the liver-fluke, so that the liming of the fields may produce an increase of the liver-flukes in the human population.

As the soil is a colloidal aggregate containing many colloids, the reactions of acidity and basicity are not so simple as they are in true solutions.

Since the soil consists only to a small extent of soil solution, and to a much larger extent of substances not in solution, the effect of pH on the solubility of these substances has a great effect on the composition of soil solution. Aluminum is present in all soils, but is insoluble over a broad range of pH on each side of neutrality. It is soluble as the cation, Al^{+++}, at pH 4 and less (greater acidity) and soluble in high alkalinity as the aluminate anion; 50,000 acres of acid soil in Indiana cannot grow corn unless the aluminum ion is precipitated by phosphate (as aluminum phosphate) or by lime (as aluminum hydroxide).

Iron in appreciable concentration as ferric or ferrous salts is very toxic. It is precipitated in acid solution as the phosphate and in alkaline solution as the hydroxide. It is apparently sufficiently soluble to meet the needs of the plant in all except alkaline soils. Lack of iron may be one of the causes of failure of chlorophyll to develop (chlorosis of plants). It is possible that the root hairs of some plants may secrete acid and thus absorb iron from alkaline soils. Lack of Mg (sand drown in New Jersey) may cause chlorosis.

The addition of soluble phosphate to soils not only may serve to supply the needs of the plants for phosphorus, but may act beneficially by precipitating calcium, magnesium, barium, aluminum, iron, manganese, copper, and some other heavy metals that might be present in deleterious concentrations in the soil solution.

Soil contains certain acids, aluminum oxide (Al_2O_3), silica (SiO_2), and kaolinite ($Al_2O_3.2SiO_2.2H_2O$) which acts as an acid and is an ingredient of clay. Soil also contains so-called humus which is really a mixture of the products of protein and carbohydrate decomposition in the soil. Humus may include amino-acids and is a much stronger acid than silica or aluminum silicate. Now humus is oxidized by the oxygen of the air, hence oxygen has to be kept out in order to keep the humus in. Water tends to keep oxygen out of the soil, as when soil is swampy. Since oxygen can diffuse through air much faster than through water, oxygen is prevented from entering swampy soils, whereas if there are air channels, oxygen can go down more rapidly. In the case of rain-soaked soil the water percolates down and draws fresh (oxygenated) air after it. In that way we get oxygen in soils that are not swampy, and yet are watered. In swamps or bogs the oxygen disappears at certain depths.

How can these silicates act as acids when they are insoluble? They cannot do so directly, but in cases where there are neutral salts present the cation combines with the silicate, leaving the acid radical free. For instance, with KCl the K ion combines with the silica or silicate, leaving the Cl ion, which in turn has to be accompanied by some ion like that of hydrogen which is displaced from the colloid by K^+. For instance, you could assume the silica to be in the form of H_2SiO_3, which is, of course, $SiO_2.H_2O$. The H_2O may not be combined at the start, but it may enter into the reaction, so that you could have $SiO_2 + H_2O + 2K^+ = K_2SiO_3 + 2H^+$. The oxygen of the hydrate water has entered into the formation of K_2SiO_3 and the hydrogen has taken on a positive charge (or rather lost its electron to the oxygen) and been given off as a hydrogen ion.

There is uncertainty as to whether these are stoichiometric chemical reactions or whether this is a case of adsorption. The end-result is the same. A large sand grain acquires a layer of K ions on its surface, so it is immaterial whether they are said to be adsorbed or held by chemical union. In either case a K ion replaces an H ion—in terms of adsorption, on the surface of the particle—so that you get HCl in solution where before you had KCl. With aluminum silicate the formation might be a little more complicated, but the same principle is involved. In fact the aluminum silicate probably has more to do with the acidity of the soil than the silica. Silica tends to exist in large particles (sand). Aluminum silicate tends to break up into Al_2O_3 and SiO_2, which is more finely divided and reactive the more recently it has been formed. Aluminum silicate becomes rather strongly hydrated. Water is removed with difficulty and leaves the silicate inactive. For instance, fuller's earth, formerly used for washing clothes when soap was rather expensive, removed the dirt by adsorption. The ingredient of fuller's earth that occurs in soil is hydrated aluminum silicate, and this is a good adsorption reagent. Fuller's earth is mined nowadays and is used for decolorizing solutions. A number of workers, one of whom was Lloyd, found that certain fuller's earths were better than others. Lloyd picked out the good ones and called them Lloyd's reagent. Apparently their activity depends on the fineness of division and the degree of hydration. Fuller's earth will adsorb various substances, such as alkaloids, that being the way to obtain pure alkaloids—*i. e.*, by adsorbing on fuller's earth and dissolving off. The adsorbed alkaloid may be taken internally and is absorbed more slowly and is devoid of bitter taste. Purified vitamin B is obtained in the same manner by adsorbing it on fuller's earth in acid solution and washing off in alkaline solution.

The humus occurs partly as a colloid and partly in true solution as a rather weak acid, though much stronger than SiO_2. It is found that if soil is treated with KCl solution and filtered an acidity of the filtrate greater than that of the soil solution is obtained, as shown either by titration or by the hydrogen electrode method. This indicates an ionic exchange of K^+ for H^+ from the soil (as discussed above). Other ions also are exchanged for H^+ and for one another. If KCl solution is mixed with the soil about 0.1 to 1.3 per cent. of the weight of the soil in the form of calcium may go into solution. This action is not purely an ionic exchange. If it were, the electric charge on the soil particles would remain the same. The electric charge of finely divided silica is negative in certain solutions near the neutral point, and the negative charge is increased 50 per cent. by adding KCl to the solution, indicating that more Cl^- is adsorbed than K^+. Now if sodium acetate is added instead, the negativity is increased 100 per cent., which would show that the hydroxyl ions resulting from hydrolysis of the alkaline salt are adsorbed. The ionic exchange differs with the electrolyte added. For instance, KCl displaces more Ca ions from the soil particles than does K_2SO_4, but the K_2SO_4 displaces more H ions. $CaCl_2$ exchanges Ca ions for H ions.

There is another influence of the hydrogen-ion concentration of the soil, and that is on its granulation or flocculation. There is a relation between the pH and the power of the soil to hold water, a power probably depending on the iso-electric point of the soil colloids. At the iso-electric point they have the lowest or zero electric charge, and hold a minimum amount of water, whereas on the two sides of the iso-electric point the water-holding capacity is increased. A good many soils are rendered untillable on account of this tenacity for water. For instance, the black waxy soils of Texas are very sticky or deflocculated, as are the adobe soils of many western States. Now many soils get too sticky to plow. That is true also of subsoil that has gotten into a state known as hard-pan, a condition in which it held water, but finally dried into a hard cake. When it dries out it is like a rock and water put on it does not penetrate easily. A chemical means has been used to loosen up these soils (which apparently are all on the alkaline side of neutrality). They may be brought nearer the iso-electric point of the colloids by addition of acid or green manure or stable manure. The effect of these is only temporary, however. Or again, sulphur may be added and the bacteria will oxidize it to sulphuric acid. Still another way is to put in an acid salt like alum which will hydrolyze to Al_2O_3, which precipitates, and sulphuric acid which neutralizes the soil acidity, or add ammonium sulphate, and the plants will absorb the ammonia leaving the sulphuric acid in the soil. By addition of acid in any of these ways these soils can be made less tenacious, though in some cases it takes a very large quantity of acid. Too much acid will make them sticky again when the acid side of the iso-electric point is reached. The stickiness is reduced by $CaSO_4$. Probably the Ca^{++} flocculates the negative colloids. Al^{+++} is even more effective in breaking up the colloid gel (Coville).

The reaction of the soil has an influence on the bacteria inhabiting it. The more important ones are the nitrifiers, those that produce nitrate or nitrite.

THE HYDROGEN-ION CONCENTRATION OF NATURAL WATERS

Of course, the water of the soil is "natural water," but as it is so intimately connected with the soil we considered it separately. The pH of bog water, or pools in bogs, may be as low as 5. The pH of running streams may reach 8.3. The pH of the Seine shows a daily rhythm of 7.2 to 9.5. The pH of ordinary drinking-waters runs from 6.8 to 8. This latter reaction is favorable for the existences of the bacteria of typhoid fever and cholera. Fish are sensitive to hydrogen-ion concentration, different species having different ranges of sensitivity. For instance, Lepomis

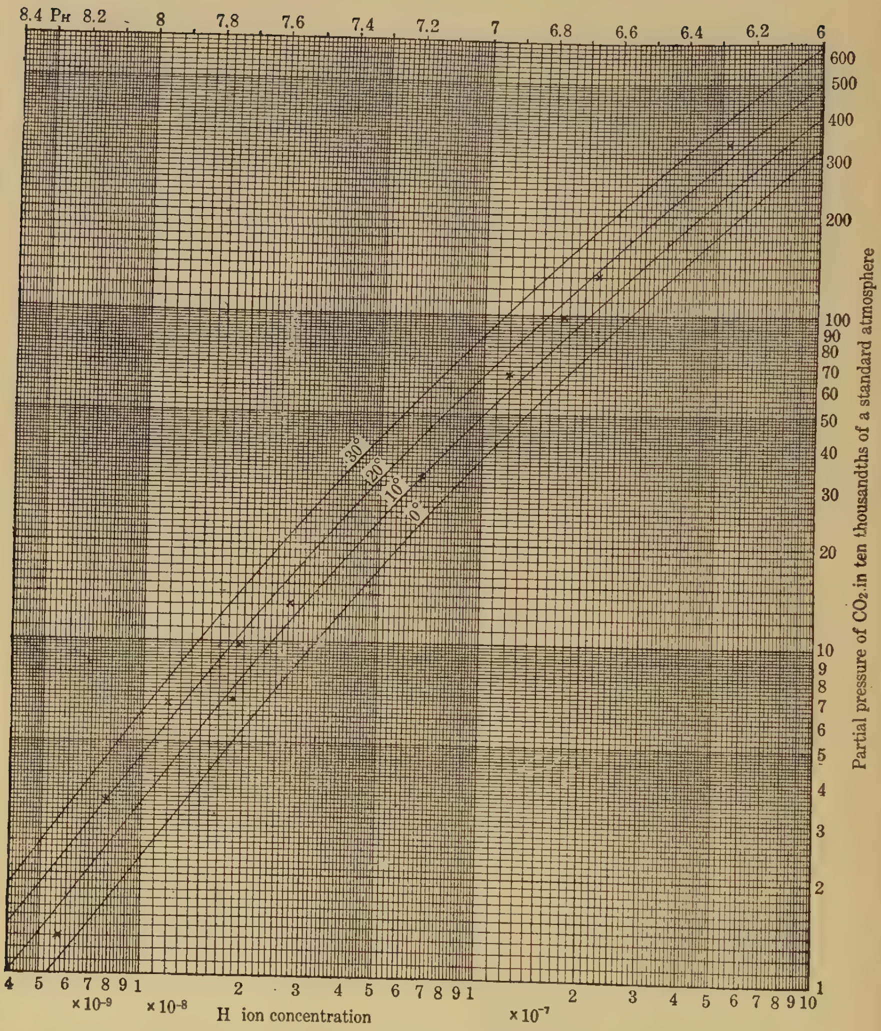

Fig. 19.—Relation of logarithm of the CO_2 pressure to the logarithm of the hydrogen-ion concentration in sea-water at 0°, 10°, 20°, and 30°, plotted on logarithmic paper.

humilis has a range of 6.6 to 7.7; Votropis cornutus has a range of 7.3 to 8.5. As a rule fish avoid acid regions.

A considerable number of studies have been made on the hydrogen-ion concentration of sea-water by Sörensen, Palitzsch, and others. Their contributions have been too numerous for detailed consideration.

Sea-water, like blood-plasma, contains a mixture of carbonates and bicarbonates. When such a solution is in contact with an atmosphere containing CO_2 the relation of hydrogen-ion concentration, bicarbonate concentration, and CO_2 pressure is shown in the accompanying chart (Fig. 19).

Sea-water of the open ocean contains, as a rule, carbonates of normality 0.0024. Dilution with distilled water decreases this value, and concentration by evaporation increases it. The *p*H of the open sea is almost constant.

Charts made at different stations from San Francisco to Samoa gave a *p*H of 8.2 to 8.25. The *p*H of the deep ocean water from the Bahamas to Nova Scotia was found to vary from 8 to 8.25. In shallow water, or partly diluted water, the values for the *p*H are lower. The accompanying table shows the *p*H for various hours of the day for a certain station in shallow water in the Gulf of Mexico (Tortugas, Fla.). The variation is due to the fact that if the water is so shallow that light can penetrate to the bottom, there occurs a marked diurnal variation because of the action of light on the sea-weed attached to the bottom, decomposing the CO_2, the *p*H rising during the day to a maximum around 3 P. M., and falling during the night with a minimum around 6 A. M. In the deep oceans floating plants cause smaller diurnal variations, amounting to a *p*H of about 0.01. Figure 20 shows the *p*H of the Gulf Stream on a trip north. The black lines represent the passage during the nights. North of Cape Hatteras the route did not follow the Gulf Stream.

Palitzsch found that the *p*H was greater at the surface than in deeper waters. Atkins found that in certain tide pools with plants in the sunlight you might get a *p*H of 9.4. This killed Caranium when the water was 27° in two and one-half hours, showing that you can have an alkalinity toxic to plants. The interior of the plants, according to Atkins, was nearly neutral with a *p*H of 6.6 to 7.3. Of course, this would involve the crushing of the plant in taking samples. Gail found the range for Fucus to be between *p*H 7.2 and 8.4. Ulva had a wider range.

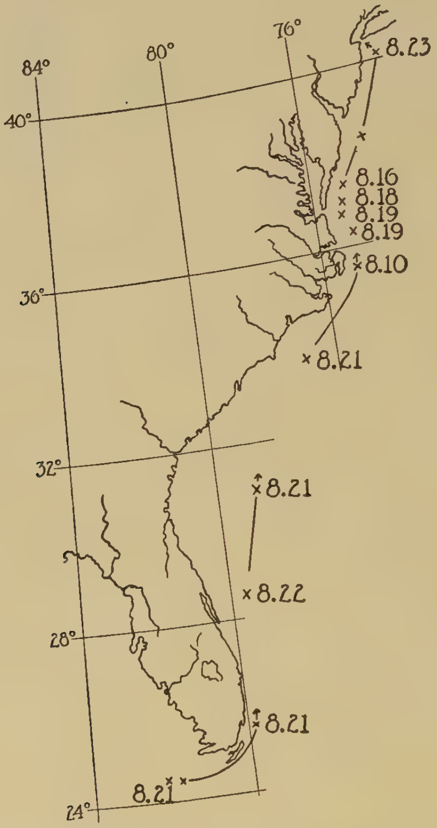

Fig. 20.—The *p*H of the surface of the ocean determined during a trip north from the Florida Keys to New York. The black lines represent the passage of the vessel between 6 P. M. and 6 A. M. It may be noted that off the lower Florida coast in the early morning the *p*H in the Gulf Stream was 8.21, and in the late afternoon it was 8.22, this increase being due to a photosynthetic action of floating sea-weed. Above Cape Hatteras the path of the vessel is far removed from the Gulf Stream and the water is much diluted with river water.

The chart given above shows variations of *p*H with temperature. Cold water, at equilibrium with air (that would give a pH OF SEA-WATER AT TORTUGAS, FLA.

Date.	Time of day.	Temp.	pH.	Total CO$_2$	CO$_2$ tension.	O$_2$ per liter.	O$_2$ saturation, excess or deficiency.
July 9..	6^{h}30^{m}a. m.	28.1	8.20	44.55	3.2	4.26	−0.27
9..	6 00 p. m.	29.1	8.28	43.34	2.6	5.97	+1.52
10..	5 30 a. m.	28.2	8.20	44.55	3.2	3.96	−0.57*a*
10..	6 30 a. m.	28.4	....	.....	...	4.21	−0.30*a*
10..	8 30 a. m.	28.8	....	.....	...	4.47	−0.01*a*
10..	10 00 a. m.	29.2	....	.....	...	4.90	+0.45*a*
10..	11 00 a. m.	29.6	8.25	43.8	2.9	5.2	+0.79*a*
10..	12 00 noon.	29.5	8.25	43.8	2.9	5.2	+0.78
10..	1^{h}30^{m}p. m.	29.7	8.26	43.65	2.8	5.2	+0.80*a*
10..	3 15 p. m.	30.0	8.26	43.65	2.8	5.6	+1.22*a*
10..	4 15 p. m.	30.2	8.27	43.50	2.7	5.8	+1.44*a*
10..	5 15 p. m.	29.5	8.27	43.50	2.7	5.5	+1.08*a*
10..	6 15 p. m.	29.0	8.26	43.65	2.7	5.43	+p.97*a*
10..	7 00 p. m.	28.8	8.26	43.65	2.7	5.13	+0.65*a*
10..	9 00 p. m.	28.3	....	.....	...	4.52	0.00*b*
11..	2 50 a. m.	28.1	....	.....	...	4.25	−0.28
11..	5 50 a. m.	28.0	8.22	44.3	3.0	4.13	−0.41
11..	6 30 a. m.	28.2	....	.....	...	4.20	−0.32
11..	2 10 p. m.	30.0	8.26	43.65	2.8	5.2	+0.82
11..	4 30 p. m.	29.5	8.26	43.65	2.8	5.3	+0.88
12..	6 45 a. m.	28.6	8.23	44.15	3.0	4.35	−0.14
12..	12 15 p. m.	30.5	8.25	43.8	2.9	5.3	+0.96
12..	4 00 p. m.	30.5	8.27	43.5	2.7	5.3	+0.96
12..	5 00 p. m.	30.2	8.27	43.5	2.7	4.97	+0.61
13..	6 30 a. m.	28.1	8.18	44.9	3.4	4.12	−0.88*c*
13..	12 30 p. m.	29.5	8.25	43.8	2.9	4.85	+0.43*c*
13..	5 20 p. m.	29.7	8.26	43.65	2.8	4.85	+0.45*c*
14..	5 45 a. m.	28.3	8.20	44.55	3.2	4.5	−0.02*c*
14..	4 00 p. m.	29.5	8.26	43.65	2.8	4.73	+0.31*c*
15..	6 00 a. m.	28.2	8.21	44.4	3.1	4.14	−0.39*c*
15..	4 20 p. m.	29.8	8.28	43.34	2.6	4.5	+0.10*c*
16..	6 45 a. m.	28.0	8.21	44.4	3.1	4.4	−0.14*c*
16..	4 15 p. m.	29.8	8.27	43.5	2.7	4.84	+0.44*c*
17..	6 25 a. m.	28.0	8.20	44.55	3.2	4.33	−0.23
17..	4 55 p. m.	30.1	8.27	43.5	2.7	5.00	+0.63
18..	6 00 a. m.	28.0	8.20	44.55	3.2	4.28	−0.26
18..	4 00 p. m.	30.0	8.25	43.8	2.9	4.85	+0.47
19..	5 20 a. m.	28.1	8.21	44.40	3.1	4.30	−0.23
19..	4 05 p. m.	29.4	8.24	44.00	3.0	4.62	+0.19
19..	4 30 p. m.	29.3	8.24	44.00	3.0	4.84	+0.44
19..	5 00 p. m.	29.3	....	.....	...	4.93	+0.49
19..	5 40 p. m.	29.7	....	.....	...	4.87	+0.43
19..	6 05 p. m.	29.9	....	.....	...	4.97	+0.58
19..	6 30 p. m.	29.7	....	.....	...	4.84	+0.44
19..	6 45 p. m.	29.4	....	.....	...	4.89	+0.42
19..	9 35 p. m.	28.6	8.22	44.30	3.1	4.45	−0.04
20..	6 15 a. m.	28.0	8.21	44.4	3.1	4.35	−0.19
20..	6 20 a. m.	27.9	....	.....	...	4.40	−0.15
20..	6 55 a. m.	28.0	....	.....	...	4.37	−0.17
20..	8 25 a. m.	28.4	8.22	44.30	3.0	4.58	+0.07
20..	9 25 a. m.	28.6	....	.....	...	4.67	+0.18
20..	10 30 a. m.	28.9	....	.....	...	4.58	+0.11
20..	11 30 a. m.	29.0	8.22	44.30	3.1	4.73	+0.27
20..	12 15 p. m.	29.2	....	.....	...	4.70	+0.25
20..	2 00 p. m.	28.9	8.22	44.30	3.1	4.70	+0.23
20..	3 30 p. m.	28.7	8.22	44.30	3.1	4.70	+0.22
20..	6 10 p. m.	29.8	8.24	44.00	2.9	4.70	+0.22
21..	5 45 a. m.	28.0	....	.....	...	3.94	−0.60*d*

a Unusually calm. *b* Sudden squall. *c* Rough weather. *d* Squall.

pH of Sea-water at Tortugas, Fla.

Date.	Time of day.	Temp.	pH.	Total CO$_2$.	CO$_2$ tension.	O$_2$ per liter.	O$_2$ saturation, excess or deficiency.
July 21..	6^h30^ma. m.	27.9	8.20	44.55	3.0	4.12	−0.43
21..	9 30 a. m.	28.2	8.20	44.55	3.2	4.50	−0.02
21..	11 40 a. m.	28.7	....	.....	...	4.63	+0.15
21..	2 36 p. m.	29.4	8.22	44.30	3.2	4.63	+0.20
21..	4 30 p. m.	29.1	8.22	44.30	3.1	4.61	+0.16
21..	6 20 p. m.	29.2	8.23	44.15	3.0	4.77	+0.33
22..	5 20 a. m.	28.2	8.22	44.30	3.0	4.13	−0.39
22..	9 15 a. m.	28.6	....	.....	...	4.55	+0,06
22..	2 30 p. m.	29.6	8.25	43 80	2.9	4.76	+0.35
22..	4 30 p. m.	29.2	8.25	43.80	3.0	4.68	+0.23
22..	6 15 p. m.	29.0	8.23	44.15	3.0	4.60	+0.14
22..	9 30 p. m.	28.7	....	.....	...	4.32	−0.16
23..	5 40 a. m.	28.2	8.20	44.55	3.2	4.07	−0.45
23..	6 45 a. m.	28.2	....	.....	...	4.15	−0.37
23..	8 45 a. m.	28.7	8.21	44.40	3.2	4.62	+0.13
23..	10 45 a. m.	29.3	8.24	44.00	2.9	4.76	+0.32
23..	12 10 p. m.	29.9	....	.....	...	4.77	+0.38
23..	2 10 p. m.	29.8	8.25	43.80	2.9	4.87	+0.47
23..	3 55 p. m.	29.5	8.25	43.80	2.9	4.81	+0.39
23..	5 45 p. m.	29.2	8.23	44.15	3.0	4.72	+0.27
23..	7 10 p. m.	28.9	....	.....	...	4.55	+0.08
23..	9 10 p. m.	28.7	8.21	44.4	3.2	4.30	−0.17
24..	2 30 a. m.	28.5	8.21	44.40	3.2	4.15	−0.35
24..	4 50 a. m.	28.3	8.20	44.55	3.2	4.10	−0.42
24..	5 40 a. m.	28.3	8.20	44.55	3.2	4.15	−0.37
24..	7 35 a. m.	28.5	8.22	44.30	3.1	4.31	−0.19
24..	12 40 p. m.	29.8	8.25	43.80	2.9	4.88	+0.48
24..	3 30 p. m.	30.4	8.24	44.00	3.0	4.77	+0.42
24..	4 45 p. m.	29.9	8.23	44.15	3.1	4.76	+0.37
25..	5 30 a. m.	28.6	8.21	44.4	3.3	4.04	−0.45
25..	10 00 a. m.	29.0	8.22	44.3	3.3	4.60	+0.14
25..	11 30 a. m.	29.6	8.26	43.65	2.8	4.72	+0.31
25..	12 15 p. m.	29.8	8.26	43.65	2.8	4.72	+0.32
25..	2 35 p. m.	30.6	8.26	43.65	2.9	4.87	+0.54
25..	4 20 p. m.	30.3	8.26	43.65	2.8	5.29	+0.93
26..	6 15 a. m.	28.5	8.22	44.30	3.3	4.22	−0.28
26..	12 40 p. m.	29.4	8.24	44.00	3.1	4.86	+0.43
26..	4 15 p. m.	29.8	8.20	43.80	2.9	4.82	+0.42
27..	6 40 a. m.	28.3	8.20	44.55	3.5	3.82	−0.70
27..	1 40 p. m.	30.5	8.25	43.80	3.0	5.26	+0.92
27..	3 50 p. m.	30.7	8.25	43.80	3.0	5.06	+0.73
28..	6 15 a. m.	28.5	8.20	44.55	3.5	4.10	−0.40
28..	1 30 p. m.	30.5	8.26	43.65	2.8	5.10	+0.76
28..	2 50 p. m.	30.5	8.26	43.65	2.8	5.20	+0.86
28..	5 45 p. m.	30.2	8.27	43.50	2.7	4.78	+0.42
29..	6 30 a. m.	28.7	8.22	44.30	3.3	4.18	−0.30
30..	5 30 a. m.	28.8	....	.....	...	4.42	−0.06

CO$_2$ pressure of 0.03 per cent. of an atmosphere), would have a lower *p*H value than warm water. The sea controls the CO$_2$ content of the air; the air does not control the CO$_2$ and *p*H of the sea, for there is 30 times as much CO$_2$ in the sea (as carbonates) as in the air. Plants floating on the surface of the water act as a blanket to hold the CO_2 within the sea. If they were not there the pH at the surface would be the same as at great depths, and some CO_2 would diffuse into the air to give a new CO_2 value to the atmosphere. The shallow water and the diluted water near shore undergo great changes in pH. Cameron found that the straits of Georgia and the regions adjacent to the Frazier River in British Columbia change greatly in pH with the seasons of the year. The summer water was much more alkaline than the water of other seasons. Legendre observed an even greater variation of pH. Gaarder made a map of the variations in Norwegian waters.

HYDROGEN-ION CONCENTRATION OF THE URINE

Urines are of two types in regard to hydrogen-ion concentration: first, phosphate solutions, mixtures of mono- and dibasic phosphates, which occur on typical carnivorous diets, and second, carbonate solutions, which occur on typical herbivorous diets. Both phosphates and carbonates are strong buffers. It is very fortunate that phosphates do not occur in appreciable amounts in alkaline urines, otherwise the passages of the urinary apparatus would become clogged with insoluble phosphates. Mammals, of course, might have evolved a secretion of solid urine, just as have birds (which excrete uric acid crystals with a little fluid between). But in birds a fluid urine is secreted and the water is reabsorbed. Ordinarily we think of the supersaturation of any solute in the urine as presenting favorable conditions for urinary calculi.

If the ash of the diet that is burned in the body is acid the phosphoric acid is excreted largely in the urine; but if the ash of the diet that is burned in the body is alkaline the phosphoric acid is largely excreted in the intestine as Ca or Mg phosphate.

It is possible to titrate the phosphates in the urine. Acid, to the turning-point of methyl orange or brom-phenol-blue, must be added to reduce the phosphate to the monobasic phosphate. It may then be titrated with alkali to the turning-point of phenolphthalein, in which case the phosphates change to the dibasic phosphates. The number of gram equivalents of alkali equals the number of gram molecules of phosphoric acid. There is one disturbing factor, however, which robs this titration of a quantitative value, that is, the presence of ammonia. Since the greater the acidity of the urine, the greater the ammonia content, ammonia would have to be eliminated before titration could be carried out. Other weak electrolytes, like beta-hydroxybutyric acid, have the same disturbing effect.

We might say that ordinarily in human urine the *p*H varies from 5.6 to 7.4. During fasting it is at the acid limit with a *p*H of 5+ because the diet is really the body proteins, liberating phosphoric acid on combustion. The foods that have an acid ash when burned in the body are the animal foods and cereals. Other foods (including milk and all plant foods except some seeds) have an alkaline ash.

There are various other factors that influence the hydrogen-ion concentration of the urine. For instance, a sweat bath increases the acidity of the urine. Of course, the urine should be taken without loss of CO_2. As one can readily see, the CO_2 is present in large amounts only when the urine is alkaline or neutral.

Bacteria in the urine may change the *p*H. In the absence of sugar Bacillus coli does not produce acid, and the final *p*H is about 8. It is possible to have urine so acid as to allow no growth of bacteria. Bacillus coli is inhibited from growth in urine of *p*H 4.6 to 6.5 on the acid side and 9.2 to 9.6 on the alkaline side. The typhoid bacillus has narrow limits.

After increased gastric secretion, as when a large meal is undergoing digestion in the stomach, there is an increase of the bicarbonate of the blood, which, in turn, results in a decrease in the acidity of the urine. While the pancreatic juice is being secreted in large amounts it is probable that the reverse effect occurs.

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CHAPTER XI

IONIC EQUILIBRIA IN BLOOD

The blood-plasma and serum are nearly the same in respect to ion concentration, and hence data on both may be considered simultaneously, and adult human blood is referred to unless otherwise stated. Perhaps the ion in the serum whose variations have been most studied is the Ca ion. The data, however, usually refer to the total Ca of the serum, and Von Meysenbug has shown that only 60 to 70 per cent. of it is diffusible, whereas Neuhausen and Marshall found only 20 per cent. ionized. In the micromethod Ca is precipitated as oxalate and titrated with permanganate. Perhaps not quite all of it is precipitated. The washing is never perfect and undoubtedly some protein remains and is titrated as Ca. Perhaps these two errors balance each other, as Clark asserts that the same values are obtained as with the ashing method on larger samples. The average values are about 10 milligrams of Ca per 100 cc. of serum, Mazzocco finding 9.2, Billigheimer 9.3, Briggs 9.6, Halverson, Mohler, and Bergeim 10.2, and Groves and Vines 10.5. In the rat Kramer and Howland found 10, and Goto found 8 in the rabbit, whereas Greenwald found more than 15 in the dog. In the parturient mother Bogert and Plass found 9.1, and Mazzocco 8.8. In the infant Jones and Nye found 12.3, and Mayer 11. In children Denis and Talbot as well as Jones and Nye found 10, Steethman and Arntzenius 12.5. Bogert and Plass found 9.1 in maternal and 10.9 in fetal serum. The value may be greatly reduced in rickets, tetany, epilepsy, and chorea.

Richter-Quittner state that there is no Ca in the erythrocytes of man, ox, cat, dog, horse, or rabbit under normal conditions, a conclusion supported by the classical analyses of Abderhalden, but disputed by some investigators. Since the blood contains

60 to 70 per cent. by volume of plasma we should expect it to contain about 6 to 7 milligrams of Ca per 100 cc. The values found are from 6 to 9 milligrams, indicating that the corpuscles may contain Ca.

The corpuscles of the ox and sheep contain about 1 milligram Mg per 100 grams, and other animals larger amounts, and the serum of various mammals, including man, about 2.5 milligrams according to Abderhalden and Briggs, whereas Bogert and Plass found 2 in maternal and fetal serum.

Since phosphoric acid exists in a non-dissociated condition in lecithin, nucleoprotein, and some other compounds, many attempts have been made to determine the inorganic P. The number of milligrams of inorganic P per 100 cc. of serum was found by Briggs as well as Eddy and Heft to average about 3, whereas Bloor found 2.8 for men and 3.5 for women. Bogert and Plass found about 4.5 in parturient women and 7 in the fetus. Denis observed retention in cases of cardiorenal disease, and the value may be increased to 15 shortly before death. Howland and Kramer observed 5.4 in normal infants and 1.9 in cases of rickets. Hess and Matzner observed a decrease in the inorganic P in the blood of infants during the late winter.

The number of milligrams of Na per 100 cc. of serum is about 300 according to Abderhalden, Briggs, and Greenwald for man and other mammals. Neuhausen and Marshall found only about 200 in dogs.

The Na content of the corpuscles is only about half that of the serum and may be even lower.

The K content of the serum is about 32 mg. per 100 cc. in human blood according to Schmidt, but Briggs finds it only 20, and Abderhalden and Greenwald 20 in mammals. The K content of erythrocytes varies from 60 to 600 mg. per 100 grams in different mammals according to the older analyses of Abderhalden. It is always very much higher than in the serum.

The Cl content of the serum is about 360 mg. per 100 cc. according to Briggs, Smith, Whitehorn and Harding, and Mason, which corresponds to the older analyses of Schmidt, but in mammals it varies from this figure to 400. Carlson, Greer, Luckhardt, and Becht found 396 in the serum and 426 in the lymph. Denis and Sisson raised it to 432 in serum by feeding NaCl. The Cl in the erythrocytes is only one-third to one-half as concentrated as in the serum, according to Abderhalden.

Denis found the inorganic sulphate in normal human blood to average 0.0005 *N*. In uremia there was retention up to twenty times the normal value. There was retention for three hours after intravenous injection in normal dogs. It should be noted that phosphates and sulphates, which Denis found to be retained in uremia, pass through membranes more slowly than do chlorides.

Ever since the time of the compensation dialysis experiments by Michaelis and Rona to determine the concentration of the diffusible constituents of the blood-plasma, many methods have been applied toward the solution of this problem, the results of some of which are given above. It was shown by McClendon that if plasma is forced through an ultrafilter the diffusible constituents pass into the filtrate, but that substances may be held back until the difference in the osmotic pressures on the two sides of the membrane equals the filtering pressure applied. If the filtering pressure is negligible, the concentration of the diffusible substances in the filtrate is nearly the same as in the original plasma. It was also pointed out that the cerebrospinal fluid is an ultrafiltrate of the blood when first formed, and that the inorganic substances are not likely to undergo great change in concentration by contact with the walls within which the fluid is contained. Therefore the concentration of the inorganic constituents of the spinal fluid may be considered the same as the diffusible portion of these substances in the blood-plasma. The sodium, potassium, and chlorine of the plasma is to a very large percentage diffusible, but the Ca is only about 50 to 70 per cent. diffusible.

The bicarbonate in serum may be titrated with the hydrogen electrode (Fig. 9, p. 96) without dilution, or with an indicator provided sufficient water is added to dilute the proteins so that they do not make the indicator useless. Van Slyke used neutral red or phenol red as an indicator. In order to increase the sharpness of the end point the serum may be diluted twenty times, an excess of standard acid added, and the CO_2 blown out with CO_2-free air in the rotating flask (Fig. 21). The excess of acid may be titrated back with standard alkali. Since the proteins may bind base the titration figure (alkaline reserve) depends on the

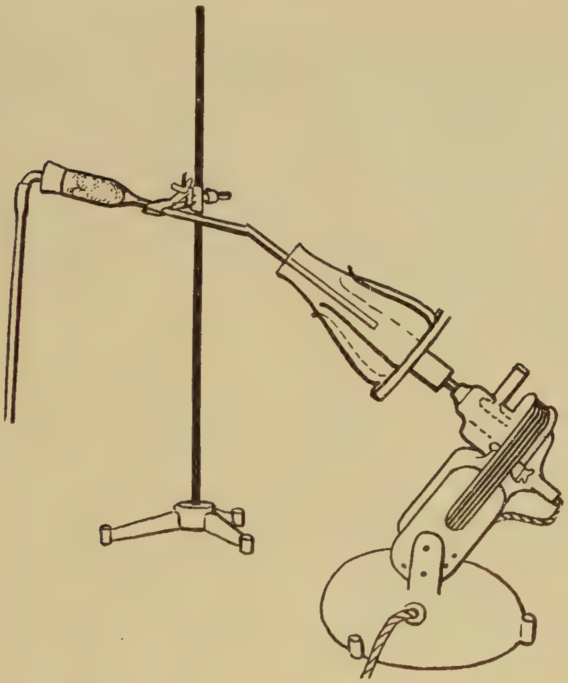


Fig. 21.—Apparatus for rotating a pyrex flask into which CO_2-free air is blown for the removal of CO_2 from blood-plasma after the addition of an excess of standard acid. (From Journal of Biological Chemistry.)

pH of the end point. If the end pH is about 7.35, the alkaline reserve in the healthy individual is about 0.03 N.

The concentration of Ca in Ringer-Locke's solution is less than the total blood-plasma Ca, and 20 per cent. more than that of the diffusible plasma Ca. Tyrode reduced it somewhat in his perfusion fluid. The K content of Ringer-Locke's solution is about correct from this standpoint, being about the same as that of the plasma.

Percentage Concentration of Diffusible Salts

	NaCl.	KCl.	$CaCl_2$.	$MgCl_2$.	$NaHCO_3$.
Ringer-Locke.....	0.9	0.042	0.024		0.02
Tyrode...........	0.8	0.02	0.02	0.01	0.10
Serum...........	0.65	0.04	0.02	0.01	0.33

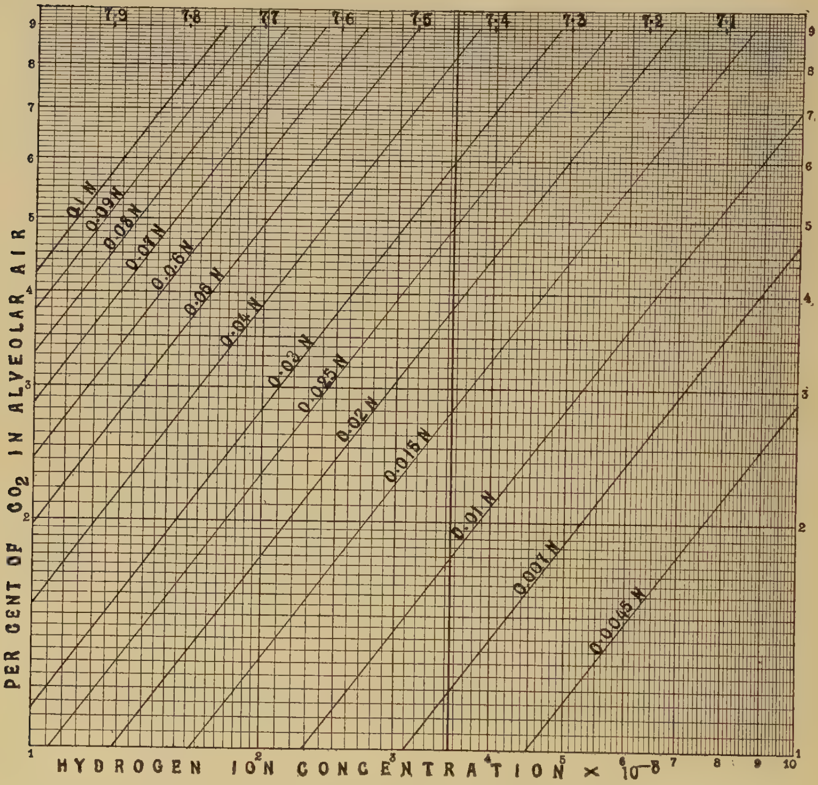


Fig. 22.—Relation of the logarithm of the hydrogen-ion concentration to the logarithm of the CO_2 pressure in blood-plasma. Each curve is for a different alkaline reserve. The alkaline reserve is expressed in terms of a normal solution of bicarbonate. (McClendon in Abt's Pediatrics, vol. i.)

The Chart given in Fig. 22 is approximately correct for blood-plasma. The buffer in highest molal concentration in the blood is bicarbonate. Later will be described a complicated reaction between the bicarbonate and other buffers in which, from the standpoint of the *p*H, the latter step in and exchange places with bicarbonate; but we may regard the curve as similar over certain distances to that of a bicarbonate solution.

The CO_2 in the alveolar air determines the CO_2 pressure in the blood because there are about 90 square meters of surface in the lungs and only about 5 liters of blood in the body that is spread out and circulating, all of the blood passing to this surface and away every minute.

The easiest way to experiment with changes of CO_2 tension is to etherize the animal and maintain artificial respiration. Then the CO_2 tension in the alveolar air may be reduced. Milroy studied that question, and found very rapid changes in the *p*H of the blood associated with the changes of CO_2 content in the alveolar air. Some of the students in this laboratory repeated the experiment and increased the *p*H of blood to 8.5 in pulmonary veins. The technic is very difficult because the heart stops beating and artificial circulation must be maintained to get high *p*H values in the arterial blood. This can be done outside of the body. By blowing air containing varying amounts of CO_2 through the blood the CO_2 tension may be increased or decreased, or by adding acid or alkali the titration figure may be altered.

Notwithstanding the possibility of varying the *p*H of the blood outside the body, its *p*H is remarkably constant inside the body because of two regulatory mechanisms. One is the kidney, which excretes more monobasic phosphate when the titratable alkalinity of the blood is reduced, and excretes carbonate when the titratable alkalinity in the blood is greatly increased. If there is not enough phosphate available for excretion when the titratable alkalinity of the blood falls, ammonium chloride is excreted, ammonia being manufactured for the purpose by some organ of the body, possibly the kidney. This mechanism stabilizes the titratable alkalinity, or, as it is called, the alkaline reserve.

The respiratory center regulates the hydrogen-ion concentration. That is to say, when hydrogen ions increase in number in the blood, the blood flowing through the respiratory center affects it in such a way that it becomes stimulated. The individual now breathes faster and blows CO_2 out of the blood, diminishing the number of hydrogen ions. If the hydrogen ions become decreased too much, the respiratory center becomes inactivated and the individual ceases to breathe—as, for instance, when one blows very hard in building a fire, one finally loses the desire to breathe. It is only a generalization, saying that the hydrogen ions in the blood cause the respiratory center to be stimulated, for we do not know that the hydrogen ions in the blood-stream itself ever reach the sensitive portion of the respiratory center. It is possible that the hydrogen ions in the blood prevent those in the respiratory center from diffusing out into the blood. If plenty of oxygen is being supplied to the respiratory center by the blood, CO_2 is probably produced, and the hydrogen ions in the center are due to the dissociation of carbonic acid. In the absence of oxygen, lactic acid is produced in muscle and in many other tissues, therefore probably in the respiratory center. Lactic acid is a much stronger acid than the carbonic acid, and hence might cause stimulation of the respiratory center. If the CO_2 tension of the blood is high, the outward diffusion of CO_2 from the respiratory center is delayed, regardless of the hydrogen-ion concentration of the blood.

The respiratory center is affected by the oxygen tension of the blood going through it as well as by the CO_2 tension, although under normal conditions the oxygen tension does not fall to the point where stimulation occurs. Under normal conditions the CO_2 tension is approximately constant. It depends upon two factors—hydrogen-ion concentration and alkaline reserve. The latter, as we have seen, is regulated by the kidney, and the former by the respiratory center. There is, then, within certain limits a quantitative relation between the hydrogen-ion concentration of the blood and the activity of the respiratory center. The accompanying chart (Fig. 22) shows that the logarithm of the H^+ concentration and also the pH (on the abscissa) are determined by the logarithm of the CO_2 pressure (on the ordinate) and the logarithm of the alkaline reserve (on a hypothetical diagonal). How do the CO_2 pressure and alkaline reserve have anything to do with the hydrogen-ion concentration? This relation, developed by L. J. Henderson, may be expressed by the formula:

$$\frac{[H^+] \times [HCO_3^-]}{[H_2CO_3]} = K$$

since

$$[H_2CO_3] \propto [CO_2]$$

by using a different value of K we may write

$$\frac{[H^+] \times [HCO_3^-]}{[CO_2]} = K_1 \qquad (1)$$

therefore

$$[H^+] = K_1[CO_2] \times \frac{1}{[HCO_3^-]}$$

This relation may be shown graphically using rectangular cartesian co-ordinates. Since K_1 is a constant, it may be omitted from the graph, provided account be taken of it in substituting numerical values for the variables. The formula then becomes:

$$[H^+] \propto [CO_2] \times \frac{1}{[HCO_3^-]} \qquad (2)$$

If $[HCO_3^-]$ remains constant it may be omitted in the same way. If $[H^+]$ is represented on the abscissa or x axis and $[CO_2]$ on the ordinate or y axis, we obtain the curve (Fig. 23).

We may modify the graph by using the logarithms of the above values. We obtain the curve (Fig. 24), assuming constant value for log $[HCO_3^-]$.

Since with $[H^+]$ constant, log $[HCO_3^-] \propto$ log $[CO_2]$, values of log $[HCO_3^-]$ may be measured on the proper diagonal from the co-ordinate origin. The complete graph is of the following form (Fig. 25).

In the graph shown in Fig. 22, p CO_2 is substituted for $[CO_2]$. This is justified by equation 5 below. [Log H^+] is the negative of pH, and hence values of pH may be marked on the abscissa.

From equation (1) we may derive the following:

$$-\log [H^+] - \log [HCO_3^-] + \log [CO_2] = -\log K_1 \qquad (3)$$

Substituting the expression pK_1 for $-\log K_1$ and pH for $-\log [H^+]$ in equation (3) we obtain:

$$pH + \log [CO_2] = \log [HCO_3^-] + p\,K_1 \qquad (4)$$

Although the mathematical relations were worked out by L. J. Henderson, Hasselbalch made a notable contribution to the experimental method by certain substitutions. It follows from Henry's law that the partial pressure p of CO_2 is proportional to

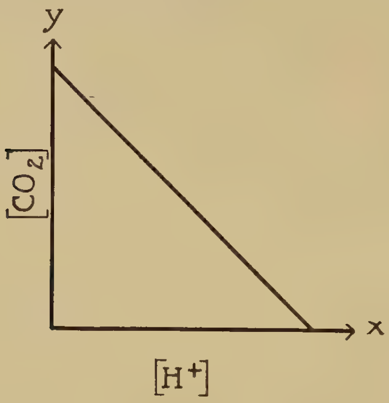


Fig. 23.—Relation of CO_2 concentration to hydrogen-ion concentration.

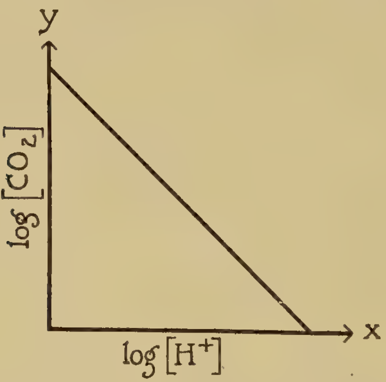


Fig. 24.—Relation of the logarithm of the CO_2 concentration to the logarithm of the hydrogen-ion concentration.

the concentration in solution. Fahr showed that the absorption coefficient of plasma for gas is 95 per cent. of that of water, and of corpuscles about 90 per cent. of that of water.

$$pCO_2 \propto [CO_2] \qquad (5)$$

It is also true that the concentration of HCO_3^- in a bicarbonate solution is very nearly proportional to the bicarbonate concentration or alkaline reserve:

$$[HCO_3^-] \propto [NaHCO_3]$$

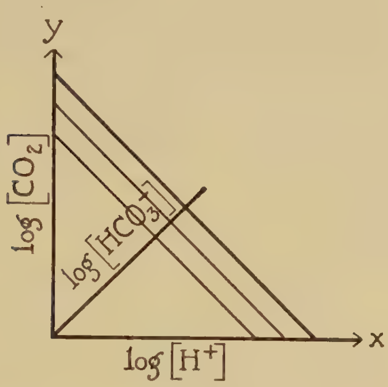


Fig. 25.—Relation of the logarithm of the CO_2 concentration to the logarithm of the hydrogen-ion concentration. Each curve represents a different concentration of HCO_3^-, and the position of these curves may be determined by measuring the logarithm of the concentration of HCO_3^- on the proper diagonal from the origin of the x and y axes.

By using a different value of pK Hasselbalch obtained the following from equation (4):

$$pH + \log (pCO_2) = \log [NaHCO_3] + p\,K_2 \qquad (6)$$

The experimental values for pK_2 obtained by Hasselbalch were obtained from whole blood. McClendon, Shedlov, and Thompson obtained results on serum that would give a value for pK_2 between 6.05 and 6.2. Van Slyke later obtained 6.12. The units are, pCO_2 in mms. Hg, $[NaHCO_3]$ in millimols per liter. Pressure of CO_2 may be written either in percentage of an atmosphere or in mm. Hg. The relation between the two is

$$\frac{\text{percentage of } CO_2 \text{ in air}}{100} \times 760 = \text{mm. Hg.}$$

The pressure (tension) of CO_2 in blood may be determined by shaking the blood with air at 760 mm. atmospheric pressure and analyzing the air for CO_2. When the atmosphere above the blood is such that no diffusion of CO_2 occurs from the plasma or the corpuscles, the tension of CO_2 in the blood is said to equal its partial pressure in the air.

By measuring this pressure the concentration of CO_2 in a bicarbonate solution is determined. The amount of CO_2 dissolved in such a solution cannot be determined directly, since only a part of it exists as CO_2. When CO_2 is dissolved in distilled water, however, conditions are less complex than in blood, since no bicarbonate is present to complicate the relations, and one would have only to determine the concentrations of CO_2, HCO_3^-, and H_2CO_3—the last two formed as the result of hydration of the first. CO_2 is present in largest amounts. $[HCO_3^-]$ can be found in distilled water by determining the H-ion concentration since these two are equal, but this number is so small, about 10^{-5} N, that it might not appreciably change the value of total $[CO_2]$. The exact ratio of $[CO_2]$ to $[H_2CO_3]$ is not known, but from theoretic consideration carbonic acid is thought to be mostly in the form of CO_2. The total can be written either in terms of CO_2 or H_2CO_3. Van Slyke expresses it as H_2CO_3, but since the greater part is present as CO_2, it seems better to express it in that form. So from the value obtained with a solution of CO_2 in distilled water, the ratio of CO_2 concentration to pressure can be obtained.

When the CO_2 diffuses into the blood-plasma, however, it meets Na^+ and HCO_3^- already present. It cannot react with either of these, for in order to satisfy electric neutrality there must be an approximately equal amount of Na^+ and HCO_3^-. Some CO_2 would become hydrated and would dissociate into H^+ and HCO_3^-, reducing the pH. For instance, the pH might be changed from the normal value of 7.45 to a value of 7.43 or some similar difference. In the meantime CO_2 has diffused into the corpuscle and dissociated into H^+ and HCO_3^-, so that at first the difference in reaction between the corpuscle and plasma would probably be negligible. The hydrogen-ion concentration increases in both cases. Other acids are present besides carbonic acid—for instance, protein acts as an acid and obeys the law of mass action.

$$\frac{[H^+] \times [Prt^-]}{[H\ Prt]} = Kap \qquad (7)$$

Kap meaning the acid dissociation constant of the protein. When CO_2 diffuses into the corpuscle and the H^+ increases, the protein ionization must decrease. Now we have another reaction—*i. e.*,

$$\frac{[Na^+] \times [Prt^-]}{[Na\ Prt]} = K_{Nap} \qquad (8)$$

Since $[Prt^-]$ decreases in equation (7), $[Na^+]$ must increase (Na Prt becoming H Prt). In brief, $[Na^+]$ and $[HCO_3^-]$ have both increased and $Na^+ + HCO_3^-$ is our formula for sodium bicarbonate. To summarize: When CO_2 enters the plasma there is an increase of $[Na^+]$ and $[HCO_3^-]$, that is to say, sodium bicarbonate in the dissociated form. The hydrogen-ion concentration increases, the sodium bicarbonate increases, and all other reactions are interlocked. The same process is happening inside of the corpuscle with hemoglobin substituted for the plasma proteins, since hemoglobin is, next to water, the chief constituent of the corpuscle.

$$\frac{[H^+] \times [Hb^-]}{[HHb]} = K_{aHb}$$

Hemoglobin forms a potassium salt.

$$\frac{[K^+] \times [Hb^-]}{[KHb]} = K_{Hb}$$

When $[H^+]$ increases, $[Hb^-]$ decreases (KHb becoming HHb), and when $[Hb^-]$ decreases, $[K^+]$ increases. We have then an increase in both $[K^+]$ and $[HCO_3^-]$. Thus more potassium bicarbonate is formed in the corpuscle. Therefore, when CO_2 diffuses into blood there is more bicarbonate formed in both the plasma and the corpuscle at the expense of the alkali protein.

The corpuscle, besides being permeable to CO_2, is also permeable to Cl^-. This may be determined by direct analysis. We assume that the corpuscle is permeable to H^+. The hydrogen ion, being the smallest and the most rapid, can probably go through any kind of membrane, such as that of the corpuscle. The buffer value of the corpuscle is greater than that of the plasma, therefore, with the same amount of CO_2 added to the corpuscle and the plasma, there would be a tendency for hydrogen ions to diffuse from plasma to corpuscle on addition of CO_2. This diffusion would cause the electric charge of the corpuscle to become more positive with respect to that of the plasma. If the interior of the corpuscle is already more negative than that of the plasma it might just reduce that negativity. At any rate, an equilibrium would be established at the boundary. Since this equilibrium is one of diffusion, any further change from equilibrium would cause diffusion to compensate for the change. In other words, if for any cause hydrogen ions go in, other positive ions must come out, or negative ions enter. Of the ions that are freed, K^+ might theoretically satisfy the first condition, and Cl^- might satisfy the second. The decision as to which moves has to be left to experiment and the experiment has been tried a great number of times. When CO_2 gas is bubbled through whole blood (or oxalated or defibrinated blood) and the blood analyzed, it is found that Cl has passed from the plasma into the corpuscle and K has not passed from the corpuscle into the plasma. The theoretic explanation of this is that the surface of the corpuscle is impermeable to K or Na ions, but is permeable to Cl ions. There are other factors on which this conclusion as to impermeability to K and Na is based, one being that the concentration of K is much greater in the cells than in the plasma, and the concentration of Na much greater in the plasma than in the cells. That same argument might be used to show that the surface is impermeable to Cl ions, since Cl ions under many conditions are more concentrated in the plasma than in the corpuscle, but the above experiment shows that this cannot be true, because Cl ions can be made to pass between the plasma and the corpuscle. Since we cannot, however, cause K ions to come out, we assume that the surface is impermeable to K ions.

There is one other possible explanation for the fact that there is an unequal distribution of the Na and K ions inside and outside of the corpuscle. It is that the dissociated ions of each are really of the same concentration in each locality, but that Na unites more readily with plasma proteins and K with hemoglobin. Several facts, however, make this explanation improbable: first, the assumption that alkali-protein both inside and outside of the corpuscle obeys the law of mass action; second, the fact that no undissociable compounds of hemoglobin and K, on the one hand, and of serum albumin and Na, on the other, have been found; and third, the lack of evidence that hemoglobin has a selective affinity for K (rather than Na) or serum albumin for Na.

It has been stated that on passing CO_2 into blood, HCO_3^- passes from corpuscle to plasma, and causes more Cl ions to pass in the opposite direction.

Oxyhemoglobin is a stronger acid than reduced hemoglobin, hence when oxygen diffuses into blood it tends to drive CO_2 out because it changes hemoglobin into a stronger acid which decomposes $NaHCO_3$ and thus liberates CO_2.

Also when CO_2 diffuses into blood the corpuscles swell. Swelling is brought about by an increase in the osmotic pressure of the corpuscle. The substances in the corpuscle capable of contributing to the osmotic pressure are H^+, OH^-, K^+, HCO_3^-, and Cl^-, and the last of these is increased by diffusion. There is an uncertainty as to whether a protein can exert osmotic pressure. Osmotic pressure in a protein solution may be due to the K ions rather than to the protein particles. Hydrogen ions are present in such small amounts that their effect on osmotic pressure is negligible.

To summarize: When CO_2 goes into the blood it diffuses both into the plasma and into the corpuscle. The corpuscle has more mineral base than the plasma. Part of the base is combined with protein, but CO_2 takes it away from the protein and forms bicarbonate. Bicarbonate ions are then more concentrated in the corpuscle than in the plasma and diffuse into the plasma since the corpuscle is permeable to them. H^+ diffuses into the corpuscle, causing a change in the electric equilibrium, with the result that Cl ions are drawn into the corpuscle. We might suppose that equilibrium could be maintained by the K^+ passing from the corpuscle to the plasma, but the corpuscle is impermeable to K^+. Now the question arises, How did potassium get into the corpuscle originally? This cannot be answered. It may be that during the growth period in the hematopoietic tissue the corpuscle wall was permeable to K^+, and now is impermeable. This does not seem a very satisfactory solution, as we shall see later when we come to the subject of permeability.

The corpuscle swells, water passing from the plasma to the corpuscle, because the osmotic pressure of the corpuscle increases more rapidly than that of the plasma. The osmotic pressure may be calculated by Donnan's equation. A simple case would be to take a protein solution on one side of a membrane and water on the other, and add to the system HOAc. It is immaterial whether the HOAc is added on one side or on the other because the membrane is permeable to HOAc—in fact, to everything except protein and protein compounds. The protein reacts with the HOAc, forming a protein acetate, which dissociates into protein^+ and OAc^-. The HOAc becomes H^+ and OAc^-. At equilibrium the undissociated molecules of HOAc are equal on the two sides and we have the equation for the two sides,

$$\frac{[H^+] \times [OAc^-]}{[HOAc]} = K$$

Since both HOAc and K are the same in each case we can leave them out of the equations, and write $[H^+]_1 \times [OAc^-]_1, = [H^+]_2 \times [OAc^-]_2$. If the products on the two sides are equal and the two factors (H^+ and OAc^-) are not equal, then the sum of the factors (H^+ and OAc^-) is greater on one side than on the other. These sums determine the osmotic pressure, which, therefore, is greater on the side where the protein is located.

Simplified case illustrating Donnan's equilibrium:

Assume K of lactic acid = 0.0001 (in a normal solution of lactic acid).

Let (1) and (2) represent conditions on two sides of a membrane, with protein present in (1) in addition to the lactic acid.

Let

	(1)		(2)
$[H^+]$	$= 0.001\ N$	$[H^+]$	$= 0.010\ N$
$[lac^-]$	$= 0.100$	$[lac^-]$	$= 0.010$
$[H\ lac]$	$= 1.000$	$[H\ lac]$	$= 1.000$
$[prot^+]$	$= 0.099$		
Total osmotic particles	1.200 equiv.		1.020 equiv.

This case does not exactly conform to facts, but is sufficiently near the truth to show roughly the qualitative relations without the use of higher mathematics.

As there is nothing in the corpuscle to keep water from entering, the corpuscle swells considerably. It would keep on swelling and burst if it were in pure water, but its swelling merely concentrates the plasma to such a point that swelling ceases. The ratio between the diffusible ions within and without the corpuscle must conform to Donnan's equation because the protein and the cations cannot diffuse (the difference between the algebraic sums of the positive and negative non-diffusible ions inside and outside being about 0.05 N cations outside), whereas some other substances can pass through freely at equilibrium:

$$r = \frac{[H_s^+]}{[H_c^+]} = \frac{[Cl_c^-]}{[Cl_s^-]} = \frac{[HCO3_c^-]}{[HCO3_s^-]} = \frac{[OH_c^-]}{[OH_s^-]} = \frac{[SO4_c^-]}{[SO4_s^-]} \qquad (9)$$

in which r represents the Donnan ratio on the two sides of the membrane as found experimentally. The subscript s denotes the serum and c the interior of the corpuscle. The brackets represent the activity of the ions and not the concentration. Van Slyke and Hastings observed that the value of r is different for the different ions.

Space does not permit us to go into all of the mathematical relations, but some of them have been reduced to graphs. According to Van Slyke the cell volume in oxygenated blood hold-

BLOOD

Concentration of hemoglobin = 8.8 mM per liter blood.
" " serum proteins = 51 gm. " " "
Respiratory quotient = 0.82

		Arterial.			Venous.					
		Serum.	Cells.	Whole blood.	Serum.	Cells.	Whole blood.	Serum.	Cells.	Whole blood.
H_2O	cc. per l. blood	549	260	809	544	265	809	−5	+5	0.0
B	mM " " "	84.02	48.32	132.34	84.00	48.34	132.34	0.0	0.0	0.0
Cl	" " " "	59.59	20.41	80.00	58.45	21.55	80.00	−1.13	+1.13	0.0
BP	" " " "	9.20	22.70	31.90	9.09	20.73	29.82	−0.11	−1.97	−2.08
$BHCO_3$	" " " "	15.23	5.21	20.44	16.46	6.06	22.52	+1.23	+0.85	+2.08
H_2CO_3	" " " "	0.71	0.34	1.05	0.82	0.40	1.22	+0.11	+0.06	+0.17
Total CO_2	" " " "	15.94	5.55	21.50	17.28	6.46	23.75	+1.34	+0.91	+2.25
Free O_2	" " " "			0.07			0.03			−0.04
Combined O_2	" " " "		8.5	8.5		5.8	5.8		−2.7	−2.7
Total O_2	" " " "			8.6			5.8			−2.7
CO_2 tension, mm. Hg				40			47			+7
O_2 tension " "				78			34			−44
Volume, cc. per l. blood		599.7	400.3	1,000	595.0	405.0	1,000	−4.7	+4.7	0.0
pH		7.450	7.309		7.421	7.300		−0.03	−0.01	
$r = \frac{[\overset{+}{H}]_s}{[\overset{+}{H}]_c} = \frac{[\overset{-}{A}]_c}{[\overset{-}{A}]_s}$				0.7215			0.7576			0.036
Per cent A in cells				25.49			26.90			1.4
Total concentration mM per l.										2.2

ing 20.2 volumes per cent. of O_2 is 92 per cent. (of the value at pH 6.4) at pH 7.3 and 91 per cent. at pH 7.4. The greater the

absolute cell volume (hemoglobin), the less the percentage change per unit change in *p*H.

The maximum range of *p*H which can occur within physiologic limits is from 7.5 to 7.3, resulting in a change of volume of about 1 per cent. This may not cause a variation in the energy required to pump blood through the capillaries because the condition in the capillaries may be considered a steady state.

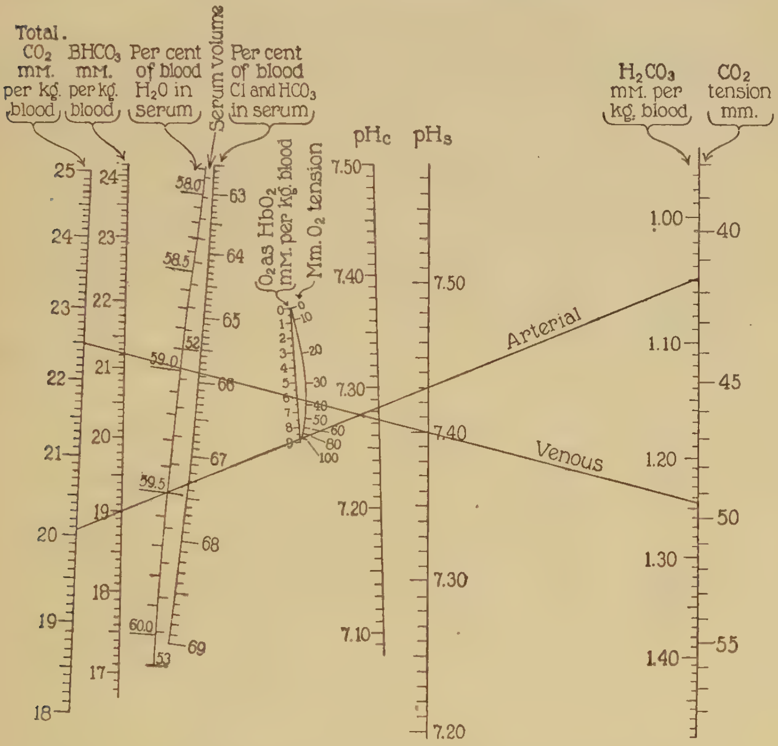


Fig. 26.—Nomogram showing the ionic equilibria of the blood, by Van Slyke and his collaborators. (From Journal of Biological Chemistry.)

In Figs. 26 and 27 are reproduced two charts called nomograms showing the calculated relationships for arterial and venous blood of average serum and cell composition as calculated by Henderson and by Van Slyke, and the tables give some of the data on which they were based. Two values fix all the others, and if a string is stretched over 2 known values all the others may be read where the string cuts the scales.

From the formula (5) above is obtained:

$$pH = pK_2 + \log [NaHCO_3] - \log (pCO_2)$$

Van Slyke has determined the variables of this equation in horse's blood, and Cullen made a number of determinations for various bloods. Van Slyke calculates a difference in the pK_2 for the corpuscles and the plasma. The total difference in pK_2 is 0.12, so that the value of pK_2 for the interior of the corpuscles would not vary far from 6.

Serum

		Arterial.	Venous.	
H_2O	*cc. per l. serum*	915.4	914.3	−1.0
B	*mM* " " "	140.1	141.1	+1.0
Cl	" " " "	99.37	98.22	−1.15
BP	" " " "	15.34	15.27	−0.07
$BHCO_3$	" " " "	25.40	27.66	+2.26
H_2CO_3	" " " "	1.17	1.38	+0.21
Total CO_2	" " " "	26.58	29.04	+2.46

Cells

		Arterial.	Venous.	
H_2O	*cc. per l. cells*	649.5	654.2	+5
B	*mM* " " "	120.7	119.3	−1.4
Cl	" " " "	50.98	53.21	+2.23
BP	" " " "	56.70	51.18	−5.52
$BHCO_3$	" " " "	12.99	14.96	+1.97
H_2CO_3	" " " "	0.85	0.99	+0.14
Total CO_2	" " " "	13.86	15.95	+2.09
Combined O_2	" " " "	21.2	14.3	−6.9

(Henderson, Bock, Field, and Stoddard.)

The question is, What is the normal pH of blood? From the data shown in Fig. 22 it may be seen that if the kidney maintains the titratable alkalinity at a certain normality, and if the CO_2 tension is maintained at a certain value, the point at which their co-ordinates cross will give the pH. It has been found that

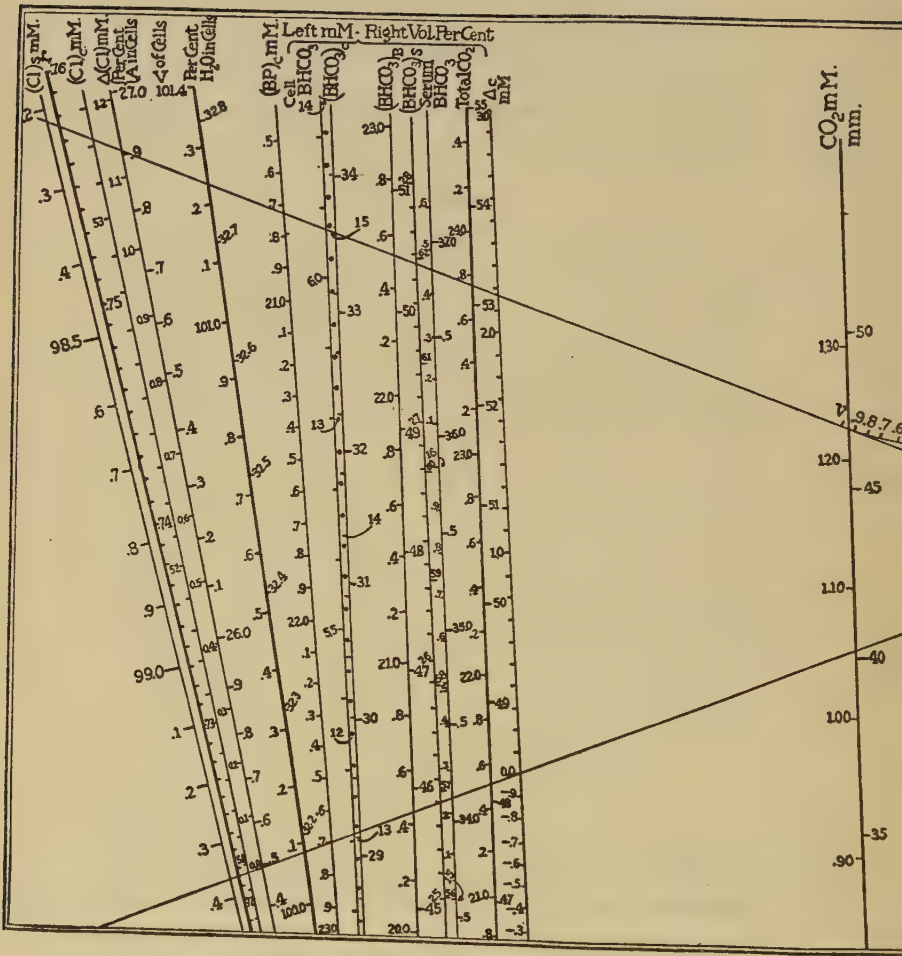
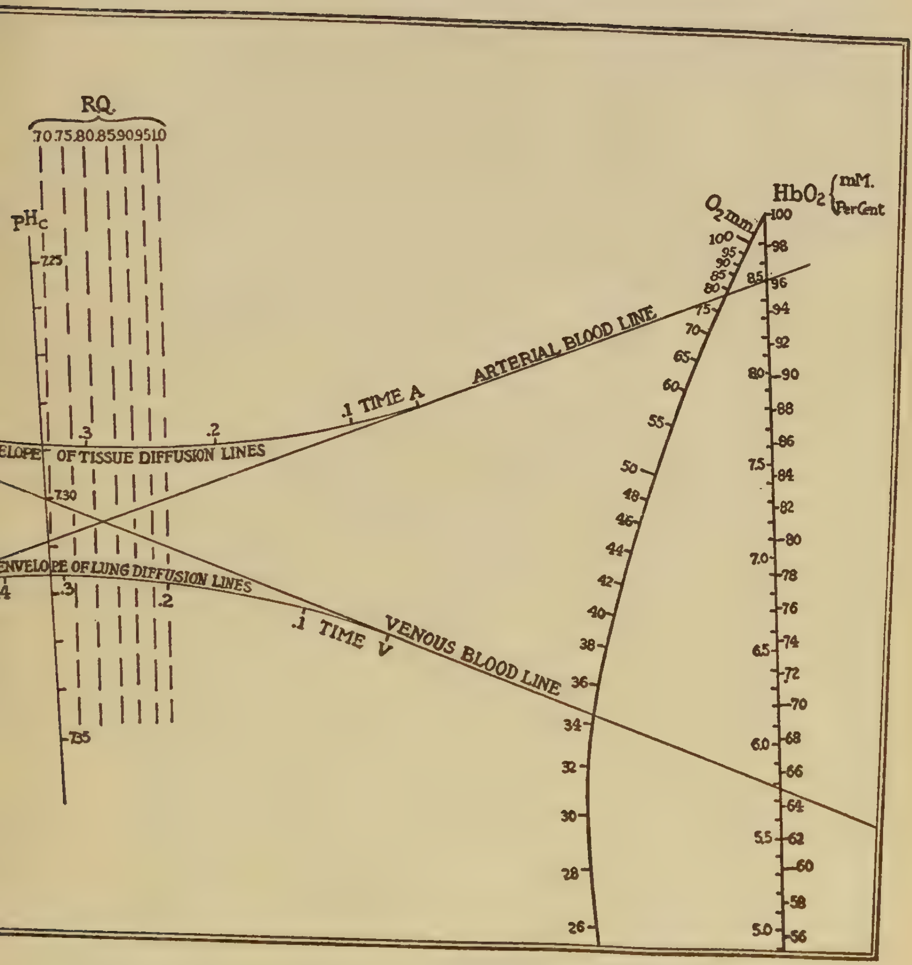


Fig. 27.—Nomogram showing the ionic equilibria in the blood, by



on and his collaborators. (From Journal of Biological Chemistry.)

the respiratory center responds so sensitively to slight changes in the hydrogen-ion concentration of the blood that it maintains the blood at a definite *p*H. That *p*H is somewhere around 7.45, although it varies slightly with different individuals and with

Estimation of the Changes Occurring in the Normal Respiratory Cycle

	Arterial.			Venous.			Changes.		
	Serum.	Cells.	Whole blood.	Serum.	Cells.	Whole blood.	Serum.	Cells.	Whole blood.
(Hb) *mM. per kg. blood*	0.0	9.0	9.0	0.0	9.0	9.0	0.0	0.0	0.0
(P), *gm.* " " "	37.0	0.0	37.0	37.0	0.0	37.0	0.0	0.0	0.0
(B) *m.-Eq.* " " "	73.0	54.0	127.0	73.0	54.0	127.0	0.0	0.0	0.0
(H_2O) *kg.* " " "	0.464	0.316	0.780	0.460	0.320	0.780	−0.004	+0.004	0.0
(Cl) *m.-Eq.* " " "	51.2	24.8	76.0	50.0	26.0	76.0	−1.1	+1.1	0.0
(BP) " " " "	6.62	22.01	28.63	6.54	19.87	26.41	−0.08	−2.14	−2.22
($BHCO_3$) " " " "	12.79	6.21	19.00	13.96	7.26	21.22	+1.17	−1.05	+2.22
(H_2CO_3) " " " "	0.626	0.426	1.052	0.733	0.510	1.243	+0.11	+0.08	+0.19
Total CO_2 " " " "	13.42	6.63	20.05	14.69	7.77	22.46	+1.27	+1.14	+2.41
Combined O_2 *mM.* " " "	0.0	8.8	8.8	0.0	6.0	6.0	0.0	−2.8	−2.8
Dissolved O_2 " " " "			0.14			0.03			−0.1
Total O_2 " " " "			8.94			6.03			−2.9
p_{CO_2} *mm. Hg* " " "	41.6	41.6	41.6	49.2	49.2	49.2	+7.6	+7.6	+7.6
p_{O_2} " " " " "	100.0	100.0	100.0	38.0	38.0	38.0	−62.0	−62.0	−62.0
*p*H	7.43	7.283		7.40	7.272		−0.030	−0.011	
Volume *l. per l. blood*	0.525	0.475	1.000	0.521	0.479	1.000	−0.004	+0.004	0.0
r ratio			0.713			0.746			+0.033
(*r*) "			0.485			0.519			+0.034
Respiratory quotient $\frac{\Delta CO_2}{\Delta O_2}$									0.83

(Van Slyke, Wu, and McLane.)

diet, and is affected by anything that affects the respiratory center. The mechanism is somewhat complicated and will be considered again later.

Besides being affected directly by the respiratory center, the *p*H is supposed to be influenced by certain other factors. For instance, it is stated that soon after vaccination the *p*H of the blood falls off to a point of neutrality, reaching somewhere around 7. It is asserted by Chambers that the *p*H of normal blood is 7.31 and that in carcinoma it averages 7.36 (because of hyperpnea accompanying pain?). The *p*H of the plasma is said to diminish during anaphylactic shock. There is a change of *p*H when serum is heated to 56°. The *p*H of the lymph and cerebrospinal fluid may change because they are filtrates of the blood-plasma.

It is asserted that the *p*H of the cerebrospinal fluid in meningococcus meningitis varies from 7.2 to 7.4 and 7.4 to 7.6, the latter being the reaction of normal cerebrospinal fluid. These values are probably too high because of salt effect on the indicator. In acute rheumatic fever the *p*H of joint exudates is said to be 7.27 to 7.42. When infected with Staphylococcus aureus the exudate has a *p*H of 6.9; with Streptococcus hemolyticus it may drop to 6.19.

When hemoglobin combines with oxygen to make oxyhemoglobin it becomes a stronger acid. (The acid dissociation constant of oxyhemoglobin is $10^{-7.16}$ and of reduced hemoglobin is $10^{-7.31}$.) Reduced hemoglobin is such a weak acid that it cannot take Na^+ away from HCO_3^-, but when oxygen enters the system it becomes a stronger acid and unites with the Na^+, leaving the HCO_3^- to go off as CO_2.

$$NaHCO_3 + HHb + O_2 \nrightarrow H_2CO_3 + NaHbO_2$$

This takes place in the body, and so aids in the transfer of CO_2. It seems that the blood has developed into a very efficient machine for carrying CO_2 and oxygen. The same molecule of hemoglobin acts as an agent for carrying them both; although the hemoglobin may not combine with CO_2 to any extent, it unites with Na^+, and when CO_2 comes into the blood the Na^+ goes over to the

CO_2 forming bicarbonate. Doisy found that 53 per cent. of the CO_2, of the blood is carried without change of *p*H—merely by reduction of oxyhemoglobin to hemoglobin.

Now we come to the question of what is called acidosis. For a long time this condition was recognized as a symptom of disease, though the cause was unknown. It was supposed to be due to acid intoxication or poisoning of the body by the action of free acid. Later, upon more careful determinations of the reaction of the blood, it was found that the blood was always slightly alkaline or neutral, with a *p*H around 7.45. No really proved case of acid blood-plasma has ever been found in living persons except in coma, so that view of acidosis had to be modified. It is very probable that acids occur inside of cells; in fact, the *p*H inside of the red cells is probably about 7.30, which is less than in the plasma. At any rate, in the blood there is always alkalinity. Rather recently, chiefly through the work of Van Slyke, the bicarbonate buffer of the blood has been emphasized. In the case of acidosis it was found that the bicarbonate content was greatly reduced, sometimes to one-tenth its value. In some parts of the body where acid is being produced and the buffer value has gone down, the blood may possibly not neutralize the acids. Van Slyke says that various divergences from the normal are possible. He maintains that the normal range of *p*H is from 7.3 to 7.5, and that cases occur on the two sides of that, none of them being acid. The extreme range he gives as 7 to 7.8. According to Van Slyke, tetany occurs at a *p*H of 7.8, and coma at a *p*H of 7. Van Slyke defines compensated acidosis as acidosis in which the *p*H has remained constant when the alkaline reserve is changed, because the CO_2 has varied in inverse proportion. The following different states may occur:

1. Uncompensated alkali excess, where alkali has increased in the blood with no other change except a correspondingly greater *p*H.
2. Compensated alkali excess, where there is a normal *p*H range with increased alkaline reserve.
3. Compensated CO_2 excess, the same as the above, for any compensation of the alkali occurs with CO_2, and so CO_2 may be said to be compensated with alkali.

4. Uncompensated CO_2 excess, in which pH is reduced.
5. Uncompensated CO_2 deficit.
6. Compensated alkali and CO_2 deficit.
7. Uncompensated alkali and CO_2 deficit, with pH within normal range.
8. Uncompensated alkali deficit, with pH reduced.

Besides these eight (in reality only seven) there is the normal condition. He produced all abnormal conditions experimentally.

According to Conway and Steven, the pH of the corpuscles is 0.13 less than that of the plasma. This experiment was made by laking the corpuscles.

There is a possibility of producing acidosis by feeding $CaCl_2$ by mouth. Haldane fed 85 g. in three days, and found that $CaCO_3$ was excreted by the feces and Cl was absorbed, producing acidosis. Milroy, who has measured the alkaline reserve of the blood, asserts that the alkaline reserve of the plasma is 0.024 N of which he gets 0.01 in true solution, and the rest, 0.014, would be due to the colloids present.

The hydrogen ions have some effect on the degree of contraction of blood-vessels, increase of hydrogen ions causing dilatation and decrease of them effecting contraction. This appears to be an adaptation whereby increased CO_2, which will produce H ions, will bring about vascular dilatation and cause more CO_2 to be removed. This reaction occurs with a change of pH of 0.21, which is about the normal range of Van Slyke.

It is known that acidosis occurs in anesthesia. We have already seen that anything that increases respiration throws CO_2 out of the blood, with lowering of alkaline reserve of the plasma, because Cl passes into the plasma and neutralizes some of the alkali. But according to Van Slyke this explanation is not sufficient, in ether anesthesia the pH falling to 7.2 to 7.3, alkaline reserve to 0.06 to 0.016, and CO_2 tension to 10 to 25 mm. (about 40 mm. being normal). As a result of quantitative determinations Van Slyke figured that the changes are not due entirely to increased breathing, but to the entrance into the blood of some acid other than CO_2. This might be lactic acid.

In epilepsy there is an increase in ammonia of the blood. In case of periodic vomiting it has been found that an alkalosis occurs, or an increase of buffer in the blood, which is improved by large doses of 0.1 *N* HCl. Cholera for a long time was supposed to be accompanied by acidosis (Sellards.)

In shed blood it has been demonstrated that glucose changes into lactic acid. Of course, in the body that same change would produce acidosis. Glomerular insufficiency causes acidosis.

The HCl secreted by the stomach is taken from the blood, with consequent increase of alkaline reserve of the blood; and the reverse process may take place either during the resorption of HCl by the intestinal wall or during the excretion of bicarbonate by the pancreas. Enough time elapses between the secretion of HCl by the stomach and the secretion of alkali by the pancreas to cause a temporary alkalosis in the blood, so that a change in urinary secretion occurs and the urine becomes either alkaline or less acid. During overexertion lactic acid is produced in the muscles so rapidly it cannot be burned, hence the alkaline reserve of the blood is reduced and there is a condition of acidosis. But if only part of the muscles are active while others are at rest, and the same blood is circulating through the resting muscles, the lactic acid may be burned.

A good deal of work has been done in regard to high altitudes. Men climbing the Alps for the first time may have mountain sickness, which is due to lack of oxygen. Following this there is an increased production of lactic acid, partly from exertion and partly from lack of oxygen to burn it. Therefore the alkaline reserve is lowered, causing increased breathing in order to regulate the CO_2 balance; the CO_2 carrying power of blood is decreased, consequently the blood has to circulate more rapidly and the CO_2 tension of the alveolar air is reduced. The resulting stimulation of the respiratory center brings about greater ventilation and greater O_2 intake.

The low alkaline reserve and high *p*H in fever is probably due to hyperpnea or increased breathing (Koehler).

Smooth muscle in the intestinal musculature as well as in blood-vessels is sensitive to changes of *p*H. Though these muscles are stimulated by the Na_2CO_3, the question is not settled as to whether the stimulation is due to the Na ion, the HCO_3 ion, or the OH ion. Probably it is a summation of effects. Such a summation of effects might be illustrated by a perfusion experiment with the heart of a marine invertebrate (conch). Sea-water is used as the perfusing medium instead of blood. Sea-water contains Na^+, Ca^{++}, K^+, and Mg^{++}, the proportions of which may be varied without change of osmotic pressure. Certain modifications affect rate of beat, while others influence force. These may be summarized in the following diagram:

$$\text{Rate}\left\{\begin{array}{l}\text{Increase } Na^+,\ K^+,\ OH^-\\ \text{Decrease } Mg^{++},\ H^+,\ Ca^{++}\ \text{(apparently)}\end{array}\right. \qquad \text{Force}\left\{\begin{array}{l}\text{Increase } Ca^{++}\\ \text{Decrease } Na^+\end{array}\right.$$

Ca^{++} is extremely toxic and can be increased only gradually. Finally, with sufficient increase of any one, the heart stops beating. The stopping may occur either in systole (contraction) or diastole (relaxation,) depending on which ions occur in excess according to the following diagram:

$$\text{Stopping in}\left\{\begin{array}{l}\text{Systole—}Na^+,\ K^+,\ OH^-\\ \text{Diastole—}Mg^{++},\ H^+,\ Ca^{++}\\ \text{Rigor mortis—}Ca^{++}\end{array}\right.$$

Maximum force requires a delicate balance of ions. Small amounts of Ca^{++} markedly increase the force.

If K^+, which increases the rate, is given in too large proportions, the heart becomes paralyzed and the rate drops to zero. So really, in a simple qualitative study, stopping has to be considered as a third element. For continued maintenance of both rate and force H^+, OH^-, Na^+, and Ca^{++} are all essential, and certain others help to maintain the heart in a normal condition. Whether the HCO_3 ion is necessary is hard to say because it is produced by the tissue, and hence is present in any experiment.

Another instance of variations of normal balance of ions might be cited in cases of tetany. Tetany may be produced experimentally in animals by increase in the ratio:

$$\frac{a[Na^+] + b[K^+] + c[OH^-]}{u[Mg^{++}] + v[H^+] + w[Ca^{++}]}$$

whereas relief from tetany may be brought about by a decrease in this ratio. In this ratio, a, b, c, u, v, w, are proportionality factors. Greenwald injected $NaHCO_3$ intravenously and produced tetany. Tetany may also be obtained by forced respiration, which, according to Grant and Goldman, increases the concentration of OH ions. Mathews in 1905 observed that H^+ is the only monovalent ion capable of antagonizing the effect of Na^+.

Cameron and Collip have determined the alkaline reserve of blood of lower animals, and find it rather low in the pigeon, approximately equal to that of man in other birds, and less again in the frog. These values vary, however, some being equal to, and all approaching that of man. When it comes to the lower vertebrates the alkaline reserve of the lamprey is very low, also of the shark family and bony fishes. Among invertebrates the jelly-fish and other Cœlenterates have hardly any. The same is true of star-fish and other Echinoderms; it is a little higher in Crustaceans and Mollusks. So we really have to come to the vertebrates above the fishes to get a condition approximating that in man.

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Ionic Equilibria in Blood

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CHAPTER XII

OSMOSE

OSMOTIC PRESSURE OF CELLS

It has been supposed that after an animal cell has remained in a medium until equilibrium is established, the osmotic pressure of the cell is the same as that of the medium, and hence Hamburger, in order to determine the osmotic pressure of blood-cells, placed them in different media and found the medium in which they would not change in size. He then determined the osmotic pressure of that medium. Plant cells are surrounded by a cell wall of considerable strength, and if they are placed in a medium of higher osmotic pressure than their own the protoplasm shrinks away from the cell wall. The osmotic pressure of the cell is supposed to be the same as that of the medium that just fails to separate protoplasm from the cell wall (plasmolysis). It has been determined, however, by Collip that the osmotic pressure of blood-cells as determined by the freezing-point method is about 10 per cent. lower than that of the serum, and the difference in twenty-two determinations averaged 400 mm. of mercury. We should suppose, therefore, that the blood-cell is a mass of protein that would swell in plasma if it were not for the semipermeable membrane surrounding it, that the osmotic pressure of the plasma or serum presses out water from the protein gel, and that the elasticity of the gel prevents water being pressed out to osmotic equilibrium. This finding would elucidate the observation of F. H. Scott, that when water is added to blood all of the water passes into the corpuscles. The corpuscle proteins have not swollen to their maximum and they greedily absorb any additional water.

It is difficult to determine the exact point at which the corpuscle freezes, and work like that of Collip is sometimes puzzling.

Collip found that the osmotic pressure of muscle, spleen, lung, and heart of a dog as determined by the freezing-point method was about 20 per cent. higher than that of the blood-plasma of the same dog. In this case the tissues were ground in a meat chopper, and it is possible that lactic acid, which is produced under such conditions, may have raised the osmotic pressure. It would certainly seem strange if the osmotic pressure of the blood-cells is lower than that of the blood-plasma and the osmotic pressure of the tissue cells greater than that of the blood-plasma. The osmotic pressure of the blood-serum of mammals corresponds to a freezing-point of about −0.6°. The depression of the freezing-point, Δ, in blood-serum of various animals is given in the following table:

	Depression of freezing-point in degrees.
Mammals:	
Man, serum	0.48–0.655
Ox	0.53–0.66
Horse	0.564
Pig	0.6–0.615
Rabbit	0.55–0.665
Dog	0.55–0.65
Cat	0.638–0.69
Rat	0.619
Sheep	0.575–0.621
Whales, blood	0.65–0.7
Birds:	
Pigeon	0.633–0.69
Fowl	0.6–0.652
Goose	0.55
Turtles:	
Caretta caretta, marine	0.61–0.69
Colpochelys kempi, marine	0.70
Chelonia mydas, marine	0.675
Chelonia caouana, marine	0.602
Emys europæa, fresh water	0.46–0.65
Pseudemys elegans	0.48
Amphibia:	
Rana palustris	0.44
Rana esculenta	0.465–0.56
Bufo viridis	0.76
Salamandra maculata	0.479

	Depression of freezing-point in degrees.
Teleosts (bony fishes):	
Charax puntazzo, marine	1.04
Cherna gigas, marine	1.035
Crenilabrus parvo, marine	0.75
Box salpa, marine	0.85
Pleuronectes platessa, marine	0.65–0.85
Amia calva, land locked	0.508
Anguilla vulgaris, fresh water	0.58–0.69
Barbus fluviatilis, fresh water	0.48–0.56
Catostomus teres, fresh water	0.51–0.52
Leuciscus dobula, fresh water	0.45
Perca, Cyprinus, Tinca, Esox, fresh water	0.512
Perca fluviatilis, fresh water	0.5–0.51
Salmo trutta and alpinus, fresh water	0.62
Ganoids:	
Acipenser sturio	0.76
Lepidosteus osseous	0.49–0.52
Polyodon spathula	0.486–0.50
Invertebrates (excepting marine) (blood + body juices):	
Anodonta cygnea	0.2
Astacus fluviatilis	0.8
Dytiscus marginalis	0.57
Hirudo medicinalis	0.4–0.43
Dragon flies	0.65

Other vertebrates show a more variable osmotic pressure, but the values are not far different, their freezing-points being from 0.45 to 1. Marine invertebrates have an osmotic pressure equal to that of the sea-water, but in fresh-water invertebrates it is less. In certain diseases the osmotic pressure of the blood-plasma or serum may be outside the normal range.

Harris and Gortner have made numerous determinations of the osmotic pressure of the pressed juices of various plants. It was found that in the same plant the osmotic pressure increased with the height above the ground. It is the osmotic pressure of the cells in the leaves that draws water from the vascular bundles. The water is drawn up through the tubules (tracheæ) in the vascular bundles by adhesion to the walls and cohesion of the water. The cohesive force, or tensile strength, of the water is the equivalent of 50 to 200 atmospheres. If an air-bubble gets into a tracheid, it expands and fills it, displacing the water (Dixon). High osmotic pressure seems to be a defense against drying out in the case of desert plants. Harris, Gortner, Hoffman, and Valentine found a specimen of Atriplex nuttallii growing near the Great Salt Lake that had a freezing-point of $-14.4°$, equivalent to an osmotic pressure of 169 atmospheres. They find in species of cactus very low osmotic pressures. In these cases we may assume a more or less approximate equilibrium between the water vapor tension of the atmosphere and the vapor tension of the surfaces of the plants. Since they are both growing in the same atmosphere, these two plants would have about the same vapor tension in their surface layers. The cactus is surrounded by a wall impermeable to water, but there are some stomata. The cactus holds the CO_2 produced by respiration during the night for photosynthesis during the day, and hence needs to open the stomata only for an excess of CO_2 for growth. It may grow new parts for years while resting on a dry shelf in a museum, but this is done at the expense of the older parts. It seems probable that the colloids in the cactus have power to hold water and yet do not depress the freezing-point, just as in case of the erythrocyte (Collip).

It was shown by Bachmann and Runnstrom that the fertilized frog's egg has a very low osmotic pressure and that the osmotic pressure rises during development. They found that the ovarian egg had a much higher osmotic pressure. The lowering of the osmotic pressure is due to outward diffusion of crystalloids, as will be shown below.

ELECTROPHORESIS (CATAPHORESIS)

By cataphoresis or, as it should more properly be called, electrophoresis is meant the migration of solid particles in an electric field. The forces concerned are the same as those causing the movement of ions in electric conductivity. It has been determined that the speed of migration at constant fall of potential is determined by the charge on the body divided by its surface area. Since we do not know the surface area of ions this rule cannot be applied to them. The rate of migration of colloidal particles is stated to be, however, of the same order of magnitude as the speed of ions (Zsigmondy, 1917). Under a potential gradient of 1 volt per centimeter colloidal silver moves toward the anode 2 to 3.8 μ per second, and colloidal gold about 4, and the chlorine ion, 6.8 at room temperature. Factors influencing the rate of movement were studied by Billitzer (1903). Among substances usually electronegative there are, besides the colloidal metals, glass, shellac, clay, carborundum, asbestos, wool, cotton, arsenic sulphide, and sulphur, whereas chromic chloride, cobalt oxide, zinc oxide, and barium carbonate are ordinarily electropositive. According to Coehn (1910) the substance with higher dielectric constant is the more positive of two phases in contact. According to this rule all substances in water would be negative. Other factors besides dielectric constant influence the charge, which may be reversed by changing the pH and by other means. Not only colloidal solutions, but emulsions and suspensions, may show cataphoresis. A new process for the extraction of cod-liver oil is the mincing and salting of the livers and removal of the oil by cataphoresis. The mincing does not destroy all the plasma membranes, however, which are destroyed by the heaping up of ions (polarization) due to the current.

The methods of studying cataphoresis are different from those used in electric conductivity, as the individual particles may be observed under the microscope. Since the walls of the vessel are charged, the water surface will be charged in an opposite sign, and hence the water will be carried along the surface of the vessel. This surface current of water disturbs conditions in the surface layers, and hence it is necessary to focus with a microscope down some distance into the liquid. The distance at which the effect of the walls is manifest is given at 25 $\mu\mu$ (Bancroft, 318), but in the absence of opposing forces the whole mass of liquid moves. The advancing edge of a whole mass of particles too small to be seen individually may be observed if the particles are colored or if they absorb or disperse a large part of the light falling on them. Particles that cannot be observed in this way can be observed by ultraviolet light which causes them to fluoresce, as Svedberg has shown.

It is found that proteins do not migrate at the iso-electric point, or, to put it more exactly, they migrate only to a slight extent and equally in both directions (see Chapter IX). On the alkaline side of the iso-electric point they migrate toward the anode because they are negatively charged, and on the acid side of the iso-electric point they migrate toward the cathode because they are positively charged. Substances in the living cell migrate when the cell is placed in an electrostatic field, that is to say, when it is immersed in a water solution through which a current is passed. It was shown by McClendon that various bodies in the cells of both plants and animals migrate toward the anode, and are, therefore, negatively charged. The chromosomes and the whole nuclei migrate, as well as various granules and what might be called hyaloplasm. It seems that everything of a protein or lipoid nature migrates toward the anode, since a clear blister containing very little or no stainable substance may appear under the plasma membrane toward the cathode.

The whole cell in its natural condition usually migrates toward the anode when free to move. Exceptions have been observed in case of a few animal and possibly a larger proportion of plant cells. This would be expected of plant cells living in a variable medium, since the charge on the cell may be reversed, for instance, by certain ions. In Chapter XIII, on Permeability, it is assumed that the resting plasma membrane is permeable to hydrogen ions, but impermeable to the anions of some acid produced in cell metabolism, the retention of an excess of anions giving the cell a negative charge. In this case the hydrogen-ion concentration would have to be higher within the cell than outside of it. If the hydrogen-ion concentration should be increased outside the cell, the sign of the charge would be reversed. This actually happens, the iso-electric point of erythrocytes being about $p\mathrm{H} = 4.7$ under ordinary conditions. The charge on the cells might be pictured, however, as due to dissociation of H ions from carboxyl groups of compounds in the cell surface or might be due to adsorption of ions. Adsorption might explain the fact that trivalent metal ions easily reverse the charge on the cell.

The iso-electric point of blood-corpuscles depends not only on the hydrogen-ion concentration but also on the concentration of other ions, as shown by the following data from Haffner:

Percentage NaCl in medium.	*p*H at iso-electric point of erythrocytes.
0.025	4.4
0.250	3.8
0.750	3.4

Since the medium was buffered with acetates, other ions were present. Haffner observed the same relations with the stroma or ghost of the corpuscle.

The sedimentation of erythrocytes may be influenced by their electric charge. When brought near their iso-electric point they clump together and settle to the bottom more rapidly. The ions of heavy metals or rare earth metals cause neutralization (or reversal) of the electric charge on erythrocytes, with consequent agglutination and precipitation. Fahraens attributes the rapid settling of maternal blood-corpuscles during pregnancy to the high fibrinogen content which reduces the electric charge on the corpuscles.

Washing the corpuscles with isotonic sugar solution causes agglutination, probably because of the *p*H. Radsma found that addition of ions retards the agglutination, the effectiveness being:

$$\text{Citrate} < SO_4 < \text{acetate} < Cl < Br,\ NO_3 < I < SCN \text{ and } K < Na < Li < Ca < Ba$$

ELECTRO-ENDOSMOSE

The movement of the suspended particle in an electric potential gradient is relative to the water, and if the particle is held mechanically, the water will move in the opposite direction to the previous movement of the freely suspended particle. For instance, fine particles of glass are usually negatively charged when suspended in water, and hence go to the anode in an electric field, but if the glass particles are placed in a heap in a furnace and heated to the point of sintering, that is to say, to the point at which they adhere together, but do not melt, they will form a porous mass. If this porous mass be used as a membrane separating two bodies of water and an electric field set up, the water will go to the cathode through the membrane. This movement of water is known as electro-endosmose.

The rate at which the water moves is the same as the rate at which the particles moved when freely suspended, but in the opposite direction. The size of the pores makes no difference in the rate of electro-endosmose unless the movement is opposed by a counterpressure, in which case the core of the water in a large pore will not move at the same rate as the water next to the wall of the pore. The rate of movement of the film of the water next to the wall of the pore is not influenced by the size of the pore. If the pore is sufficiently small it carries along all of the water in the pore at the same rate. The fact that water moves in very small pores at the same rate as in large pores is taken advantage of in the drying of peat by passing an electric current through it. The pores in the peat are so fine that great mechanical pressure has to be applied to press the water out of it, but it comes out easily by electro-endosmose. Unfortunately, however, this removes only the water in the pores, and water held in peat in other ways, as by colloidal swelling, is not removed by electro-endosmose.

Freundlich used the following formula for the quantity of liquid transported in unit time through a membrane of area (σ):

$$V = \frac{\sigma\, \varepsilon\, E\, k}{4\, \pi\, \eta\, l}$$

in which V equals the quantity of liquid transported when the fall of the potential through the capillary of length l is equal to E and ε equals the charge on the walls of the pores; k, the dielectric constant of the liquid; η, its viscosity, and π the ratio of the circumference to the diameter of a circle. From this formula it is seen that the greater the charge on a membrane, the greater the rate of flow, even though the driving force remains the same. Since many materials of which membranes are prepared can be ground up and gotten into suspension, and it is easier to determine the electric charge on the material when in suspension than when it is in the form of a membrane, we will not review the data on the charge of many membranes, because that can be learned from the section on Cataphoresis. If the pores are all small in the membrane, the charge can be determined by using the formula and measuring the rate of electro-endosmose, but if any of the pores are large (since there is liable to be some back pressure) the flow may be less than if the pores are all small. This difficulty does not arise in cataphoresis measurements, since both small and large particles move at the same rate.

ANOMALOUS OSMOSE

In the section on Osmotic Pressure of Cells it is assumed that a normal osmotic pressure is present. It has been shown by Bartell and his co-workers that osmotic membranes may be made of many materials if the pores are fine enough, and although he can measure only the largest pores, he is able to grade membranes roughly by this means. If some or all of the pores are sufficiently large, abnormal osmose may occur. In no case has any abnormally high osmotic pressure been demonstrated, but Bartell has observed an abnormally rapid rate of osmotic flow through the membrane with large pores. Owing to many factors involved we will not discuss this matter here, but will take up the case of abnormally low values.

A membrane with very large pores is a simple sieve, and no osmotic effects may be observed. Bartell, using sugar solutions and copper ferrocyanide membranes, observed some osmotic effects with pores about 1 μ (0.001 mm.) in diameter; it should be remembered, however, that the osmotic effects may be due to the smaller pores, since he found only 200 pores in an area of 1.54 sq. cm. to be as large as this. In collodion membranes with pores of 1.6 μ diameter he observed osmotic effects, but there were smaller pores present. The most interesting phenomena were shown by membranes of various materials, porcelain, carbon, as well as the membranes mentioned above, with pore diameters between 0.1 and 0.4 μ. In these cases the osmose of electrolytic solutions could be reduced gradually from a normal rate to zero and even to negative values by varying the electrolyte and its concentration, and also the size of the pores. Very high negative osmotic pressures were never obtained, but the negative pressures were as high as any hydrostatic pressures that ever occur in a human body. The phenomena of negative osmose had been observed by Dutrochet, Graham, Girard, Bernstein, and Flusin. Bartell's explanation of anomalous osmose is that it is a case of electro-endosmose superimposed on one of normal osmose, and if the electro-endosmose is the more rapid of the two processes, and is in the direction opposite to the normal osmose, negative osmose occurs. Since most membranes are charged negatively the water in the pores is charged positively, and will go toward the negative side of the membrane. If the anion of the electrolyte diffuses more rapidly than the cation, this will make the dilute side negative, and the electro-endosmose is toward the dilute side or in the direction opposite to the normal.

It is perhaps desirable to review here the subject of the electric potential that may be produced by unequal diffusion of two ions. To take a simple case, consider the following concentration cell:

Calomel electrode, 0.1 N KCl, 0.1 N HCl, N HCl, N KCl, Calomel electrode.

The diffusion potential between the two acid solutions may be calculated from Nernst's formula (in millivolts at 25°):

$$E = \frac{v-u}{v+u} 59 \log \frac{c_2}{c_1} = \frac{318-65}{318+65} 59 \log 10 = +39 \text{ on the left}$$

where u = mobility of anions and v of cations; c_2 = concentration of ions in concentrated solution and c_1 in dilute solution. The two diffusion potentials between HCl and KCl may be calculated by Planck's formula where v_1 and u_1 represent the speeds of H^+ and Cl^-, and v_2 and u_2 the speeds of K^+ and Cl^-, as follows:

$$E = 59 \log \frac{u_1 + v_2}{u_2 + v_1}$$

and substituting actual values for the first one is:

$$E = 59 \log \frac{318 + 65}{65 + 65} = 59 \log 3.2 = +29 \text{ on the left,}$$

and is neutralized by the second, which is + 29 on the right. Hence the total electromotive force is + 39 on the left.

Bartell and Hocker (1916) measured the difference in potential on the two sides of porcelain membranes, and observed the negative osmose which occurred when the speed of the anion was greater than that of the cation. They found that the rate of flow varied with the difference in potential so long as other conditions remained constant. In this case the charge on the membrane was negative, but they were able to decrease this charge by the adsorption of positive ions, and thus reduce it gradually to zero, and finally give it various positive values. When the charge on the membrane was positive, negative osmose occurred, and the speed of the cation was greater than that of the anion. It should be noted that in the case of negative osmose the resultant direction of the movement of ions is the same as that of the flow of water. Bartell has observed cases that he interprets as an electro-endosmose in the same direction as the normal osmose. In this case the ionic movement that is responsible for the difference in potential on the two sides of the membrane is up-stream in regard to the flow of water. Kraemer has raised the objection that the water should move along with these ions because of friction. Space does not permit the discussion of this case here, but the reader's attention is merely directed to the fact that equalization of concentration takes place in aqueous solution by diffusion, and if the solution were flowing a case could be set up in which the movement of the particles of solute was up-stream.

It is interesting to note that Bartell and Madison observed anomalous osmose with gold-beater's skin (which is prepared from animal membranes) and with calf's bladder. Bartell and Sims have used parchment paper, which is a carbohydrate membrane. Thin slices of wood have also been used. In other words, membranes prepared from organisms may show negative osmose. In these cases the osmotic pressures on the two sides of the membrane were always different.

Girard (1908–13) made experiments in which he states that the osmotic pressure on the two sides of the pig's bladder membrane was the same. For instance, with isotonic solutions of cane-sugar and tartaric acid the membrane and the saccharose solution were electropositive; the direction of the osmose was toward the sugar. In this case the cation diffuses faster than the anion. If lead nitrate was substituted for the tartaric acid, the charge on the membrane remaining of the same sign, the fall of potential across the membrane was reversed, the sugar solution being negative, and the direction of the osmose was toward the lead nitrate. The speed was reduced to one-third, which is due to the fact that the anion diffuses very little faster than the cation. When potassium carbonate was substituted for the tartaric acid and a negative membrane used, the sugar solution was found to be electropositive and the osmose was in the direction of the potassium carbonate solution. The difference in ionic speeds and rate of osmose are increased, the K ion moving faster. It was not necessary to use a non-electrolyte as similar results were obtained with tartaric acid and sodium sulphate, using a positive membrane. In this case the sodium sulphate was electropositive and the osmose was in its direction. In this case the diffusion potential was due to the H ion.

In performing such experiments it is difficult to maintain equal osmotic pressures. If the osmotic pressure is determined by the freezing-point, a difference of a few centimeters in osmotic pressure cannot be measured, and if it is determined directly by the use of a membrane, it is very difficult to find membranes that give normal values. If, however, the differences in potential are determined and the speed of the ions is known, and the result harmonizes with those in which the solute is on only one side of the membrane, there is no reason to believe that an error has been made.

Since differences in potential between two sides of living membranes, such as frog's skin or other membranes containing glands, have been shown to exist, or at least to appear during activity of the glands, it is very probable that electro-endosmose is a factor in the flow of fluid during the process of secretion. In such a structure as the stomach wall there is more than one type of membrane separating the blood from the stomach contents. It is reasonable to suppose that in one section of membrane an electromotive force is produced and that the electromotive force is not due to the simultaneous action of the whole wall. This electromotive force may be due to the difference in the speeds of the positive and negative ions just as in the cases studied by Bartell. The flow of water from the blood to the stomach contents may be a case of anomalous osmose, the driving force being the difference of potential.

There remains to examine the hypothesis given in Chapter X to explain the high acidity of the gastric contents. In the blood we have a very low concentration of hydrogen ions, and in the gastric contents a very high concentration of hydrogen ions. If sections of the membrane are permeable only to hydrogen ions and the interior of the stomach is electronegative, hydrogen ions would be drawn into the stomach contents. The return circuit would be through another section of the membrane, that is to say, through the one that gives rise to the difference in potential. If the electrolyte that diffuses into the stomach contents and gives rise to the difference of potential is sodium chloride, this would make the stomach contents negative and cause a flow of water toward the stomach contents, since we know that the membrane is negative and the chlorine moves faster than the sodium ion. (It should be mentioned that the secreting side of all glands during activity is negative as compared with the blood side.) The chlorine ions which diffuse rapidly into the stomach contents through this region of the membrane supplemented by the hydrogen ions which diffuse through other portions of the membrane would together form hydrochloric acid in the stomach contents. There is nothing quantitative about this conception, that is to say, it has not been shown that it will account for several hundred cc. of 0.1 normal hydrochloric acid, but the conditions are right for the flow of fluid, hydrochloric acid and chlorides into the stomach contents. The sodium chloride concentration in gastric juice is about 0.1 to 0.2 per cent., and of ammonium chloride about the same quantity, whereas that of KCl is usually less.

The fact that acidity or alkalinity may be produced by the passage of an electric current through a porous membrane in the same manner as by the passage of an electric current through a metallic membrane has been demonstrated by Bethe and Toropoff in 1914. They found that when an electric current of more than 1 volt is passed through a sodium sulphate solution divided by a membrane of gelatin, collodion, agar-agar, albumin, bladder, gold-beater's skin, parchment, carbon, or clay, the anode side becomes alkaline and the cathode side acidic, the membrane behaving similarly to a metal membrane. Water passes toward the cathode. Thus the water and the hydrogen ions pass in the same direction, the water, therefore, is charged positively and the membrane is negative. It may be assumed that hydrogen ions give the water its positive charge. With the porous membrane there is no means of robbing the ions of their charges, and if oxidation and reduction should be found to occur it would indicate that the membrane substance is a conductor of the first class, which is very improbable. In order to obtain a clear picture of the process it is necessary to consider the electrolytes as dissociated, and the formation of acid on one side implies that the H and SO_4 ions have been brought there and OH and Na ions have been carried away. Bethe and Toropoff found that polyvalent anions tend to maintain the original negative charge of the membrane. The effectiveness of anions in causing cathodic acidity is as follows:

$$\text{citrate} > \text{phosphate} > \text{oxalate} > SO_4 > I > Br > Cl > NO_3$$

In the experiments of Bethe and Toropoff it is probable that the sulphate anion was stopped or impeded by the membrane, and perhaps heaped up on the negative side. The hydrogen ions going through toward the negative side, together with the sulphate anions, would make that side acid. Sodium ions may have been retarded to some extent also and heaped up on the positive side, and, together with the hydroxyl ions passing through the membrane to the positive side, would make that side alkaline. In other words, the anode or positive side would contain sodium hydroxide and the negative or cathode side, sulphuric acid in the solution near the membrane. Around the electrodes the reverse process always takes place, the metal acting as a membrane.

SECRETION, EXCRETION, EDEMA, AND DEHYDRATION

Starling prepared a membrane impermeable to the proteins of the blood-serum, but permeable to the water and crystalloids, and found that the osmotic pressure of the former varies between 30 and 40 mm. Hg. Bayliss and others showed that after hemorrhage the intravenous injection of Ringer's fluid containing 7 per cent. gum arabic solution maintained the blood-volume for a considerable time. Colloids of the blood normally, chiefly protein, cannot penetrate the capillary walls as rapidly as do salts, and their osmotic pressure maintains the blood-volume. In the same way the colloids in the lymph and tissue juice and in the cells maintain their respective volumes. The force of the heart-beat counteracts the osmotic pressure of the colloids and presses some of the water and crystalloids out of the blood into the tissues and through the glomeruli of the kidneys. F. H. Scott showed that protein passes through the walls of the tissue capillaries, but the process is very slow. Since the blood and tissues are in very intimate relation through several paths (capillary walls, lymphatic vessels, walls of veins) the accumulation of fluid in the body, as in edema, is due to impairment of the efficiency of the heart or reduction of the functioning of the glomeruli of the kidney. Low protein diets may cause edema by weakening the heart. If edema is defined as the ratio of water to protein, the reduction of the protein of the body without the simultaneous reduction of the water content would produce edema. Some writers use the word in this sense, and speak of edema of the blood.

Dehydration may be considered the opposite of edema. A review of the literature on this subject is found in Marriott (1923). Bakwin and Morris observed dehydration with fever in the newborn. On giving water, both the dehydration and fever disappeared. Keith produced intense dehydration by intravenous injection of glucose or cane-sugar, but no fever occurred. Underhill and Kapsinow aggravated dehydration by oral administration of $MgSO_4$. In some cases Mg poisoning occurred.

Although the observations of Starling explain the volume of urine excreted, the concentration of the excretory products has not been elucidated. The osmotic pressure of the urine may be four times as great as that of the blood, or that of the blood may be eight times as great as that of the urine. The relative amounts of the crystalloids in the blood and urine vary within wide limits.

There is considerable evidence to the effect that the glomerular fluid is an ultrafiltrate of the blood, and that the resulting urine is affected by exchanges taking place through the cells of the convoluted tubules. Many observations have been made on the excretion of dyes. According to Hirschfelder and Bieter the urine in the tubules is usually alkaline. Rohde observed in frogs that the feeding of Na_2CO_3 aided the excretion of basic dyes, whereas the incorporation of boric acid aided the excretion of acid dyes. The *p*H of the blood or perfusate seems to affect the permeability of the kidneys. Barkan, Broemser, and Hahn perfused isolated frog's kidneys with bicarbonate-buffered Ringer's fluid of *p*H 7.6 containing 0.06 per cent. glucose and found the kidneys to hold back the glucose. Hamburger and Brinkman observed that the composition of the perfusate affected the retention of glucose. They obtained a sugar-free urine by perfusing frog's kidneys with a solution of the following percentage composition: NaCl, 0.5; $NaHCO_3$, 0.285; KCl, 0.01; $CaCl_2$, 0.02; glucose, 0.07. When fructose, mannose, lactose, raffinose, or galactose was substituted for glucose, more or less sugar appeared in the urine.

It was shown by Richards and Schmidt that ordinarily blood flows through only part of the glomerular capillaries, but that saline diuretics cause the closed capillaries to open and allow blood to flow through a greater number.

On injection of glucose intravenously it has been shown that a threshold for sugar excretion exists, but that this might possibly vary with individuals and conditions. According to Cushny, a threshold for NaCl exists.

Bernstein supposes that the direction of osmose through living membranes is determined by electro-endosmose. The walls of the pores in living membranes are electronegative, and hence the solution filling them is electropositive and would flow toward the negative side of the membrane. If we assume the membrane to be more freely permeable to H ions than to other ions, the acid side would be electronegative and the flow would be toward the acid side, *i. e.*, into the acid gastric juice and acid urine. The succus entericus bathing the inner wall of the intestine is more alkaline than the blood, and hence the flow would be toward the blood. The fact that the intestinal contents in some diarrheas are more acid than in normal condition would seem to be the cause and not the effect of the diarrhea, since the highly acid contents and rapid movements might restrict the alkalinity to the crypts of Lieberkuhn. The urine, however, is not always acid, but on a vegetable diet is usually alkaline, and the pancreatic and intestinal secretions are always alkaline.

Not only the secretion of urine, but that of other glands, offers problems the solution of which would require more quantitative data than we now possess. The following table modified from Höber shows the osmotic differences between blood and various secretions as indicated by the lowering of freezing-point, Δ:

Mammalian fluid.	Δ
Blood	0.48–0.69
Gastric juice	0.46–0.638
Bile	0.54–0.61
Pancreatic juice	0.60–0.67
Succus entericus	0.62–0.64
Milk	0.55–0.59
Cerebrospinal fluid	0.56–0.61
Spermatic fluid	0.55–0.60
Urine	0.07–2.60
Sweat	0.13–0.66
Saliva	0.09–0.49

Whereas gastric juice, bile, pancreatic juice, succus entericus, milk, cerebrospinal fluid, and spermatic fluid do not vary more from the osmotic pressure of the blood than can be accounted for by the blood-pressure, saliva, sweat, and urine vary enormously. Furthermore, milk, which is isotonic, is very different in composition from an ultrafiltrate of the blood. One-third of the osmotic pressure of cow's milk is accounted for by lactose, which is absent from the blood.

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CHAPTER XIII

PERMEABILITY

ANATOMIC EVIDENCE FOR A MEMBRANE ON THE CELL SURFACE

PROTOPLASM has long been known to show a high viscosity. It was claimed by Bütschli and Rhumbler that protoplasm is liquid and that its viscosity is due to its emulsion character. Recently this subject has been studied by the method of microdissection. Microdissection apparatus was designed independently by Barber and Burrows (1907) and by McClendon (1907). In this apparatus a needle or a fine pipet could be guided under the microscope. (The apparatus of Barber and Burrows was originally intended for isolating a single bacterium, and was therefore, suited to higher powers of the microscope.) McClendon showed with his apparatus that an ameba could be cut in two with an extremely fine glass needle without producing any noticeable reaction, or the needle could be passed through the ameba without cutting it into two pieces, the protoplasm closing behind the needle. It was concluded from observation of the resistance to the needle that the ameba is a closed bag of ectosarc containing endosarc in the sol stage. In other words, the viscosity is greater toward the surface. The more extensive work of Chambers is referred to below.

Another method of penetrating the protoplasm was introduced by E. P. Lyon. If eggs of marine animals are rotated in the centrifuge various bodies of low specific gravity are displaced inward, and others of higher specific gravity are displaced outward. They are not, however, thrown out of the egg, although the egg may be elongated by the force, thus tending to show that there is some layer on the surface which impedes their progress. Lyon's method was used by McClendon on protozoa. If paramecia are rotated in the centrifuge, the denser parts are thrown outward (in a centrifugal direction), but not ordinarily through the outer layers. The whole macronucleus is thrown outward and the chromatin of the nucleus is displaced inside the nucleus. In no case, however, was any body proved to be thrown completely out of the cell. One paramecium was taken from the centrifuge and found to contain no macronucleus. It had been, however, in a culture that was centrifuged for one week continuously at about 4000 revolutions per minute, and it is possible that a paramecium had divided during this process and that all of the macronuclear material had gone to one of the daughter-cells.

Heilbrunn used the same method in a quantitative study on the viscosity of protoplasm. It had already been shown by other workers that the mitotic spindle moves as a rigid body when acted upon by centrifugal force, and also that it resists the deforming action of a direct electric current (of voltage sufficient to displace the chromatin to one end of the resting nucleus and to carry the whole nucleus to one end of the cell). Heilbrunn showed that the viscosity increased during the presence of the mitotic figure.

Heilbronn, by use of an electromagnet with paramagnetic substances embedded in the protoplasm, studied the viscosity quantitatively.

The most extensive work was done by Chambers, who used for most of his work two fine glass needles in the microdissection apparatus of Barber and Burrows. Chambers dissected various membranes off of the surface of cells, which he believes are not part of the living protoplasm; but his results show that the surface layers of the protoplasm itself are more or less plastic solid in their resistance to the needle.

It should be remembered, however, that the needle may be resisted by surface tension. In imitating the food taking and the ejection of undigestible substances by the ameba, Rhumbler made a model of a chloroform drop immersed in water. If the chloroform drop was touched with a piece of fine glass thread, it repelled the thread with considerable force, but if it was touched with a thread of shellac, the shellac was drawn into the interior of the drop with great vigor. If the glass thread was coated with shellac and touched to the drop, it was drawn in, even being rolled up in case it was too long to go in straight; but after the shellac was dissolved off the glass thread was ejected from the chloroform into the water. The explanation of this is that water wets glass, but chloroform does not, while chloroform wets shellac, but water does not, or, at any rate, there is a quantitative difference between the adhesion in the two cases. The surface tension of water is strong enough to support a greasy steel needle. The needle bends down the surface of the water as though it were covered with a solid membrane. Colton observed a small clam supported to the surface of the water by several byssus threads. Snails crawl on the under side of the surface film of water. In the dissection of protoplasm a needle that is not wetted by the protoplasm will be resisted by surface tension, and therefore, in order to observe that the surface is in a solid state, it is necessary to use a needle of a substance that adheres to protoplasm. Chambers finds that glass needles adhere but are not drawn in—in fact, considerable force is required to press the needle through the surface layers. He also has shown that if aqueous solutions are injected into the interior of cells they may diffuse through the inner fluid portions, but are inhibited from coming out of the cell by the surface layer. Owing to the fact that Chambers has published his results in a book, the details are not given here.

The term "plasma membrane" has been applied to the hypothetic surface layer which is responsible for the semipermeability of the cell. Lund has recently studied it in Noctilucca. Quincke supposed it to be of a fatty nature. If the red corpuscles are laked, the hemoglobin and salts come out, and there remains the ghost of the corpuscle composed of stroma substance. The stroma consists of lecithin, cholesterol, and nucleoprotein, and it is supposed that these substances exist in the plasma membrane. Apparently the nucleoprotein may be stained. If it is the constituent that takes the stain it is more abundant in the nucleus of a nucleated erythrocyte. In the non-nucleated erythrocyte the stainable substance decreases with the age of the cell.

Cranner has shown that phytosterols and pectins come out of living plant cells into water or alkali or magnesium salt solutions (without death of the cell). He therefore aserts that they are on the surface, which he thinks is a mosaic of "lipoid" and carbohydrate.

PERMEABILITY OF THE RESTING CELL

The most extensive work on the permeability of the cell is that of Overton (1895–1907). Overton's work may be summarized as follows: Polar compounds (that is to say, those that ionize—even of the class known as weak electrolytes) have difficulty in penetrating into the cell. Non-polar compounds, particularly those which he found soluble in a few non-polar solvents, enter the cell with great ease. Overton and others have tested the solubility in olive oil and also in solutions of lecithin and cholesterol dissolved in benzene or other non-polar solvents. A great many exceptions have been found to Overton's work, and the generalization has been modified in various ways. For instance, it is found that these non-polar compounds as well as some polar compounds that enter living cells, besides having solubilities, mentioned above, lower the surface tension of a water-air surface. Furthermore, the partition-coefficients of these substances between water and various non-polar solvents is in favor of the non-polar solvent. Many of these non-polar substances have an anesthetic action, but others are very toxic. Overton did not find that salts enter the cell, but since, as is well known, salts are contained inside of cells, they must enter some time. It is possible, however, that they enter with extreme slowness, and that there is only a quantitative difference between their rate of entry and the rate of entry of non-polar compounds.

A great deal of work has been done on the penetration of dyes because of the ease with which they can be observed under the microscope. It was shown by Ehrlich that a dye may enter and be reduced to a colorless form. It has also been found that, as a rule, basic dyes stain protoplasm in its natural state better than do acid dyes. Furthermore, many of the acid dyes, such as the sulphonic acid dyes, are stronger electrolytes than the basic dyes used to stain living cells—that is to say, they have a relatively larger dissociation constant. It has been shown that the free base of alkaloids penetrates easily, but that the salt does not, and the same has been shown for some dyes. Literature on the penetration of dyes is very great. In some cases the cells were killed by heat before the studies were made, and such studies are concerned with the *staining* of dead protoplasm by dyes rather than with the *penetration* into living protoplasm.

Other methods have been used to study permeability. For instance, it has been shown that various cells containing a constituent that is not present in the medium do not lose any of it to the medium. Cells contain large amounts of potassium and the medium in which they live is often high in sodium. George Fahr showed that the muscle of the frog holds the potassium, so that only 6 per cent. diffuses out within six hours in an isotonic sugar solution, whereas 90 per cent. of the sodium diffuses out in the same time. It has been supposed that the potassium was in some non-polar union with the protoplasm, but such unions with proteins and fats are not known in chemistry. Furthermore, on the death of the cell, the potassium often comes out very freely. Cells have been placed in various solutions, and the composition of the solution investigated before and after introducing the cells to see if any solute passed out of the solution. In such cases it is necessary to determine that the cell volume remains constant, and also that any effects observed are not due to adsorption on the surface of the cells.

ELECTRIC CONDUCTIVITY OF TISSUES AND PHYSIOLOGIC FLUIDS

Electric conductivity is another method that has been employed for the quantitative study of permeability. It was shown by G. N. Stewart and by Bugarsky and Tangl that blood-cells are poor conductors. Early in this work cell sediments having only 2 per cent. of the conductivity of the serum were obtained by means of the centrifuge. It is difficult to get the last trace of serum from between the cells. If defibrinated blood is centrifuged at the rate of about 10,000 revolutions per minute for about twenty minutes, the corpuscles become packed so close together that the appearance of a single corpuscle is obtained. That is to say, the boundaries between the corpuscles that reflect light have disappeared and the mass looks clear. Since it is generally understood in microscopy that to observe objects made evident by their refractive index in the ordinary microscope they must be as great in diameter as half the wave length of light, we suppose from the homogeneous appearance of the centrifuged mass of cells that the thickness of the layer of serum between the cells is less than half the wave length of the light used in observation. If bodies are smaller than half this wave length, the light must be transmitted from the side, so that none of the direct rays enter the eye. In other words, the ultramicroscope must be used to make them visible.

It has been shown by a number of workers that various living cells, both animal and plant, resist the electric current to a remarkable degree. The conductivity of a cell suspension is due almost entirely to the fluid between the cells and, therefore, it is necessary to know the conductivity of physiologic fluids.

The specific conductivities of the fluids of marine invertebrates and sea-water extend over approximately the same range—0.043 to 0.052 reciprocal ohms—because their compositions are almost the same. The higher figure represents the conductivity of the water of the open ocean, while variations in its conductivity are due largely to rainfall and to additions of fresh water from the shore, especially in shallower water, as in the White Sea.

In the serum of Elasmobranchs conductivity is much reduced. The osmotic pressure is equal to that of sea-water on account of the presence of a high concentration (about 5 per cent.) of urea. In Teleosts (bony fishes) less urea is present and the osmotic pressure as well as the conductivity is reduced considerably below that of ocean water. Sumner studied the question of osmotic exchange by putting fishes in waters of different concentrations, and found that while there was some tendency for adjustment, equality was never established. The relative concentration of ions are as follows:

Sea-water contains for 100 atoms of Na, 2.2 K, 2.3 Ca, and 11.6 Mg.

Mammalian blood-serum for 100 atoms of Na, 5 K, 3 Ca, and 1 Mg.

Mammalian blood-cells for 100 atoms of Na, 150 K, trace Ca, and 0.6 Mg.

Macallum, on account of the similarity of concentration of salts in sea-water and in the blood of marine invertebrates, suggested that the blood of vertebrates also is a direct inheritance from the waters of a former geologic period, the Cambrian Sea. This postulates that the salts of the Cambrian Sea were of the same concentrations as in our blood-plasma, and that early animals enclosed part of the sea in their bodies (just as marine invertebrates do now), and that their descendants reproduced this condition of affairs in each generation. We know that the sodium and magnesium chlorides in sea-water have been increasing, and that calcium salts (and probably potassium) are prevented from increasing by the precipitation of calcium carbonate off the coasts of Florida, the West Indies, and other places (and potassium by the deposit of glauconite).

By similar reasoning it may be suggested that the salts inside the living cell are representative of the sea in some pre-Cambrian period. The cell became a closed system at an earlier period than the closure of the blood-system, and the earlier seas may have been relatively poor in sodium, as is the cell interior.

The following table gives the specific conductivities (χ) of various fluids and tissues at 25° C.:

Specific Conductivity (χ) at 25°

Sea-water	0.043-0.052
Marine invertebrates:	
Body fluid	0.043-0.052
Urine	0.046
Serum:	
Elasmobranch	0.02–0.03
Marine teleosts	0.017–0.018
Marine turtle	0.014
Fresh water turtle	0.007–0.018
Birds	0.013–0.016
Human fluids and tissues:	
Urine	0.014–0.033
Aqueous humor of eye	0.014–0.018
Bile	0.011–0.016
Lymph	0.016
Saliva	0.007-0.014
Serum	0.013

Human fluids and tissues:	
Blood	0.006
Muscle	0.006
Skin	0.005
Brain	0.004
Tendon	0.002
Fat tissue	0.0015
Muscle sheath	0.0014
Bone	0.0004
Mammalian serum	0.012–0.015
Due to NaCl	0.008–0010
Cow's milk	0.004–0.006
Whey	0.008–0.01

PLANT JUICES

Harris, Gortner, and Lawrence determined the ratio of electric conductivity to lowering of freezing-point $\left(\frac{\chi}{\Delta}\right)$ of the expressed leaf-tissue juices of a large number of plants growing under widely diversified conditions (xerophytic, mesophytic, and hygrophytic), and found a considerable variation, the ratio in herbaceous plants being about 90 per cent. higher than in ligneous. The osmotic concentrations in the ligneous plants were greater than in the herbaceous, while the specific conductivities (χ) of the latter were of a greater magnitude. This indicates that electrolytes play a more prominent rôle in the osmotic pressure of herbaceous plants than in ligneous plants in which organic compounds play a prominent rôle in the osmotic pressure.

BLOOD

Blood is a heterogeneous system, each phase having its characteristic specific conductivity. G. N. Stewart found that the corpuscles are very poor conductors. He measured the conductivity of blood, and calculated the volumes of cells and serum by means of his formula:

$$100 - \text{vol. per cent.} = \frac{\chi_b}{\chi_s}\left(180 - \chi_b - \sqrt{\chi_b}\right) \qquad (1)$$

Clerk Maxwell devised a formula for conductivity in a heterogeneous medium:

$$\Omega = \frac{2\Omega_1 + \Omega_2 + r\,(\Omega_1 - \Omega_2)}{2\Omega_1 + \Omega_2 - 2r\,(\Omega_1 - \Omega_2)}\,\Omega_2 \qquad (2)$$

in which Ω represents the specific resistance of the system, Ω_1 the specific resistance of the disperse phase ("disseminated spheres" of equal radii), Ω_2 that of the medium, and r the ratio of the volume of all the small spheres to that of the suspension. Their radii must be small compared with their distances.

Greene tested on bacterial suspensions the following form of Maxwell's formula suggested by MacDougall:

$$\Omega = \Omega_2 \frac{1 + r\dfrac{\Omega_1 - \Omega_2}{2\Omega_1 + \Omega_2}}{1 - 2r\dfrac{\Omega_1 - \Omega_2}{2\Omega_1 + \Omega_2}} \tag{3}$$

in which Ω_1 is the specific resistance of the cells; Ω_2, the resistance of the medium; Ω, the resistance of the suspension of cells in the medium, and r, the fraction of the total volume occupied by the suspended cells (assumed to be spherical). By multiplying both numerator and denominator in (3) by the expression $(2\Omega_1 + \Omega_2)$ the formula becomes the same as Maxwell's.

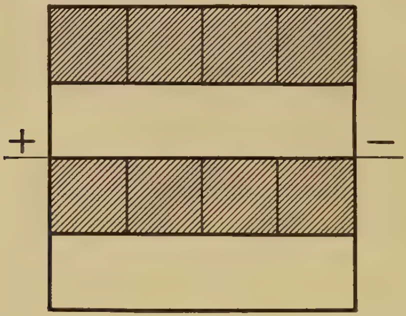

Fig. 28.—Diagram to show electric conductivity of a diphasic system with the elements of the phases arranged as resistances in parallel.

Lichtenecker and others (studying amalgams), on analogy with small cubes arranged in geometric patterns in a space lattice representing the total volume of the heterogeneous system, calculated the maximum and minimum resistances that could characterize the system. He first considered the special case in which the volume of each phase is 50 per cent. of that of the total.

The use of the calculus may be avoided by the following arrangements:

Figure 28 represents the resistance of the system at a minimum, and its value may be calculated from the formula for resistances of conductors in parallel. Therefore

$$\Omega = \frac{2\,\Omega_1\Omega_2}{\Omega_1 + \Omega_2} \qquad (4)$$

when Ω equals the resistance of the system, and Ω_1 and Ω_2 those of the two phases.

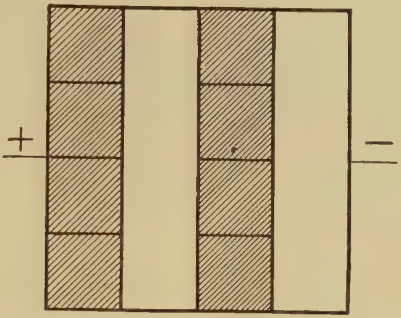

Fig. 29.—Diagram to show the electric conductivty of a diphasic system with the elements of the phases arranged as resistances in series.

Figure 29 illustrates the arrangement in which the resistance would be greatest. Its value would be derived from resistances in series and would be:

$$\Omega = \frac{\Omega_1 + \Omega_2}{2} \qquad (5)$$

When the resistances of the two phases were not greatly dissimilar, as in case of the amalgams used by Lichtenecker, and the cubes occupied one-half the space, Ω was experimentally found to be the mean of that computed in (4) and (5). When the ratio of the two phases was some other value than 1 : 1, formula 5 (maximum resistance) becomes:

$$\Omega = r_1\Omega_1 + r_2\Omega_2 \qquad (6)$$

and formula 4 (minimum resistance) becomes:

$$\Omega = \frac{\Omega_1 \Omega_2}{r_2 \Omega_1 + r_1 \Omega_2} \qquad (7)$$

for the minimum value, where r_1 and r_2 equal the ratios of the volumes of the two phases to the total volume:

$$(r_1 + r_2 = 1)$$

Hugo Fricke developed a new formula for electric conductivity of heterogeneous systems based on the assumption that the effective conductivity is the average conductivity (a volume average).

Gram and Norgaard determined the electric conductivity of blood by measuring the circuit that flowed through it with a constant voltage of 110 volts. They used a direct current, measuring the transient current within a few seconds after closing the circuit. They determined the concentration of the chlorides of the blood and that of an aqueous solution of sodium chloride of the same conductivity as the blood (NaCl equivalent of conductivity). They found that the ratio

$$\frac{\text{titrated NaCl}}{\text{NaCl equivalent of conductivity}} = 0.939 \pm 0.03$$

Increased viscosity of the solution decreases the conductivity, and Bugarsky and Tangl observed that 1 per cent. serum-protein reduces the electric conductivity 2.5 per cent.

None of the formulæ showing the relation of the conductivity of blood to the conductivity of cells and serum as affected by the cell volume are correct for high values of cell volume. Oker-Blom, Fraenckel, and recently, Gram, have drawn curves showing the cell volume on the ordinate (up to about 70 per cent.), and the ratio of the conductivity of serum to that of blood on the abscissa. Calculations may be made graphically by using such a curve.

G. N. Stewart observed that if the blood-corpuscles are injured there may be an increase in conductivity of the blood. The marked injury to the corpuscles that occurs in hemolysis causes an increase in conductivity of blood. In hemolysis many substances, including the oxyhemoglobin, diffuse out, leaving only the ghosts of the corpuscles. The ghosts of the corpuscles apparently offer very little resistance to the diffusion of ions. The oxyhemoglobin that diffuses out of the corpuscles decreases the conductivity of the blood-plasma, but this decrease is relatively small compared with the increase due to the increased conductivity of the corpuscles.

What is the mechanism of this increase in conductivity? This question may apparently be answered by the answer to another question: What causes the enormous electric resistance of the blood-corpuscle? If a blood-corpuscle is permeable to anions or cations it will conduct the electric current, and if it does not conduct the electric current it is necessarily impermeable to both the anions and the cations. Therefore the increase in conductivity must be due to greater permeability either to the anions or to the cations, or to both. Some data that we have taken up have shown that the corpuscles are permeable to chloride and sulphate ions, but the rate at which these may pass has not been measured except by the conductivity method, and the rate must be low, since the conductivity of the corpuscle is low.

When a continuous electric current is passed through blood, anions move in one direction and cations in the opposite direction. If the current attempts to pass through the corpuscles the anions and cations are retarded at the boundary of the corpuscle with those on the outside, unable to get in freely, and those on the inside unable to pass out freely, resulting in a heaping up of anions and cations at two points. From the points of entrance and exit of the current the ions tend to diffuse back so as to equalize the concentration. This diffusion-pressure produces a resistance to the current and is measured as electric resistance.

If blood-corpuscles are placed in a sugar solution the salts inside do not diffuse from them because the cations cannot get out. If the anions come out, they leave the charge of the corpuscle positive and this positive charge attracts them in again, so that as long as the corpuscle is impermeable to cations the salts will not diffuse out of it into a sugar solution. But it is probable that the anions diffuse only very slowly even when not held back by cations, since the conductivity of the corpuscle in serum is very low.

Since the corpuscle is poorly permeable to ions, the direct current does not show us whether the entire cell is non-conducting, or merely the external layer. But if the corpuscle is of the nature of a sphere with the surface non-conducting and the interior more highly conducting, there would be less impedance to the alternating current the higher the frequency. The dielectric current is limited by dielectric saturation. It can pass in one direction at any given voltage until saturation is reached. With slow alternations (*i. e.*, about 1000 cycles) the dielectric current might be insignificant. With more rapid oscillations, radio-frequency, it is well known that the dielectric current must be taken into account.

Höber attempted to determine the conductivity of the interior of blood-corpuscles by means of an alternating current, using damped waves of radio frequency. His first experiments were made with the secondary circuit constructed symmetrically with two condensers of capacity C_1 and C_2 connected in series. So long as C_1 equals C_2 the mid-point of the wire connecting the condensers should be at zero potential, but if blood-corpuscles are inserted between the plates of one condenser, the mid-point of the wire would not remain at zero potential as shown by a null-instrument.

In the second series of observations, Höber used a beaker of blood-corpuscles as the core of a solenoid in his secondary circuit, measuring the damping effect on the current at a given electromotive force and frequency. He then substituted a beaker of salt solution in which he varied the salt concentration until a similar effect was produced.

In the third series of experiments, Höber modified his circuit so he could use small quantities of blood and avoid the possibility of error due to non-uniformity of the field when the solution was used as the core of the solenoid. In this case he placed a smaller condenser in parallel with the main condenser in the secondary circuit and placed the solution between the plates of this condenser.

In a still further series of experiments Höber employed a conductivity cell consisting of a glass tube 27 cm. long with an inner diameter of 9 mm. and holding about 7.5 cc. of solution. It was connected in parallel with the solenoid instead of with the condenser of the secondary.

Höber recorded his results in terms of concentrations of NaCl which produced similar effects. At low frequencies, the conductivity of blood-corpuscles in 10 per cent. cane-sugar solution was equivalent to 0.02 per cent. NaCl solution and at high frequencies equivalent to 0.1 per cent. to 0.4 per cent. NaCl solution. Muscle gave results somewhat similar, being equivalent to 0.1 to 0.2 per cent. NaCl solutions at high frequency.

Owing to the fact that high frequency apparatus has been very much improved, and it is now possible to obtain undamped alternating currents of any desired frequency, it seemed desirable to make some new determinations. McClendon attempted to observe a difference, if any exists, between the conductivity of erythrocytes as measured by continuous currents in contrast to that measured at about one thousand cycles per second. Calomel electrodes of large size were used to prevent polarization. Automatic apparatus reversed the current every fifteen seconds and the final reading was verified during one fifteen-second interval. The electrode vessels were separated from the erythrocytes by means of agar gel made up with saturated potassium chloride solution. A Wheatstone bridge method was used. No difference in conductivity with direct current and with a thousand cycles could be established with certainty. A million cycle current was produced by an electron tube oscillator. A very simple and symmetrical bridge was constructed in which the metallic resistances were straight wires and the detector was a crystal detector and sensitive galvanometer. It was found that the specific conductivity of a sediment of ox erythrocytes washed in 10 per cent. cane sugar solution was the same as a 0.002 *N* KCl solution at one thousand cycles per second, and was the same as a 0.01 *N* KCl solution at a million cycles per second.

"Hugo Fricke has made some calculations of the capacity reactance of living cells. In order to interpret his data as capacity reactance, certain assumptions had to be made and the reader is referred to the original."

A suspension of corpuscles acts as two conductors in parallel and the admittance $Y = \frac{1}{Z}$ equals the sum of the admittances of the two conductors y_1 and y_2. The reactance of the suspension of blood-corpuscles cannot be reduced to 0 because we cannot introduce inductance inside the blood-corpuscle but the higher the frequency the less the reactance since X_L is zero and X_C varies inversely as the frequency. Therefore, the impedance decreases as the frequency increases. There is another cause for the decrease in impedance with increased frequency and this is the decrease in counter electromotive force due to the banking of ions against the dielectric. K^+ and Cl^- at 25° and about 12 volts per centimeter, move about 0.1 mm. per second. The shortest diameter of the blood-corpuscle is about 0.001 mm. Therefore, these ions traverse this distance in about 0.01 second. With a frequency of 1000 per second, nearly 5 per cent. of the ions between these two walls 0.001 mm. apart would be banked against the membrane and give rise to a counter electromotive force. With a frequency of a million, the counter electromotive force would be only 0.001 of this.

EGG CELLS

The electric conductivity of the sea urchin's egg increases when it is fertilized or caused to develop artificially. The sea urchin's egg is a single cell and when it is first extruded it resembles the blood-cell to some extent in that its electric resistance is high. That is to say, the conductivity is low. McClendon measured the electric conductivity of the sea urchin's egg at the Carnegie Laboratory at Tortugas, Florida. Although the eggs could not be packed so that there was no sea-water between them, the packing could be standardized by putting the same number of eggs in the same space by means of centrifugal force. On fertilizing the eggs there was a very marked and constant increase in conductivity. Increase in conductivity took place also if instead of fertilization with spermatozoa, the eggs were caused to develop by treating them with dilute acetic acid solution and then washing them in sea-water.

These experiments were confirmed and extended by James Gray at Plymouth, England. Instead of centrifuging the eggs, Gray kept them suspended. In numerous experiments Gray observed that both natural and artificial fertilization caused an increase in the electric conductivity of the Echinoderm egg. After about fifteen minutes the conductivity of the egg decreased, to increase again at each cell division. He went further in his experiments in order to determine the mechanism of the increase. His explanation of the mechanism is somewhat hypothetical and is as follows: Treatments of the egg that change its conductivity, such as exposure to solutions of trivalent cations or anions or to hydrogen or hydroxyl ions, cause a change of electrical polarization of the surface resulting in a change in permeability to ions. This may seem to be the reverse of Lillie's idea that the semipermeability of the membrane to ions is the cause of polarization.

MUSCLE

The electric conductivity of skeletal muscle was found by McClendon to increase about 10 to 20 per cent. on stimulation of the muscle. The muscles of the frog's thigh were placed tightly between platinum electrodes and the conductivity measured first with too little alternating current to cause contraction and then with the current increased to the tetanizing value. The technic of the experiment was complicated by the fact that when the muscle is stimulated it remains in the stimulated condition only a fraction of a second and therefore the conductivity had to be measured during this short period. The only method by which this could be done was to stimulate the muscle with the same current used in determining the conductivity. By using an alternating current the muscle was stimulated each time the current was reversed and by increasing the alternations per second the muscle could be kept perhaps 50 per cent. of the time in the stimulated condition. A source of error in the experiment is that when the muscle is stimulated it contracts and changes in shape, but the change in shape would probably not account for the large differences observed in the conductivity. Excitation without contraction was observed by Veach and Pereira, using rapid alternations. Weiss observed loss of phosphate by frog's muscle due to sub-minimal electric stimuli. According to Einthoven the contractile process is effected but the contraction is too weak to be observed.

PLANT TISSUES

The electric conductivity of marine plant tissues has been studied extensively by Osterhout and his pupils. The study of electric conductivity of these tissues of marine plants (as contrasted with other plants) is simplified by the fact that they do not show a blaze current—*i. e.*, a current of action (Waller). The electric conductivity of a leaf of seaweed, however, is not due entirely to that of the cells because the cells do not touch one another but are imbedded in a mass of agar gel or cell wall substance, the conductivity of which is probably very high. Kotte observed that the cell wall of the seaweed, Chæltomorpha, retained its normal thickness in a solution containing 4 molecules of Ca per 100 Na, but swelled to 2.5 times its normal thickness in pure NaCl solution. The distance between the cells, that is to say, the space filled with the agar gel, varies in different layers of cells of the same leaf. Osterhout did not observe a swelling in NaCl. Osterhout observed that sodium ions in pure solution of sodium salts increased the conductivity. Up to a certain point the change in conductivity was reversible, but upon greater increase death occurred. Calcium salts decreased conductivity temporarily, but upon long exposure or exposure to high concentrations the conductivity increased enormously and death occurred. The increase of conductivity in solutions of sodium salts could be reversed by addition of calcium ions. This antagonistic action extended to many ions and undissociated molecules. Na^+ and OH^- increased, H^+, Ca^{++}, La^{+++}, Ce^{+++}, Y^{+++} and Al^{+++} decreased conductivity when used within physiologic limits. Pure solutions of any salt were toxic and finally caused increase in conductivity.

Waller observed increased electric conductivity of sensitive plants during stimulation, in which state they showed a blaze current. Ebbeche and Hecht (1923) confirmed these observations.

BACTERIA

The conductivity of bacteria was studied extensively by Green. Green observed that when bacteria are killed by heat or formaldehyde in the medium in which they are grown, the conductivity of the medium is increased, and that when bacterial cells are added to fresh medium the resistance of the medium is increased. Live bacterial cells increase the resistance of the medium to a greater extent than do dead cells, but this difference is not very marked and may partly be explained by the fact that the live cells are slightly larger than dead cells. When dead bacteria that have lost salts are added the rise in resistance is proportionately much greater. When the cells are alive and have been grown in a medium containing not over 0.5 to 1 per cent. NaCl, salts cannot be washed out of them with distilled water, but salts can readily be washed out of them if they are killed. If the bacteria have been grown in a high concentration of salt, they seem to be injured by lower concentrations or by distilled water so that the salts come out of them. A typical experiment is formed as follows:

1. Grow bacillus coli on 0.5 per cent. NaCl in agar.
2. Wash the bacilli with 0.5 per cent. NaCl, centrifuge and re-wash with the same solution. Remove the precipitate of bacteria from the centrifuge.
3. Add an equal volume of 0.5 per cent. NaCl and mix thoroughly.
4. Determine the conductivity of this suspension. Also determine the conductivity of the medium from which the bacteria were separated by the centrifuge. (Green found that the conductivity of the suspension is much less than that of the medium.)
5. Heat the suspension in order to kill the bacteria and bring the temperature back to normal.
6. Determine the conductivity of the suspension of dead bacteria.

7. Separate the dead bacteria by means of the centrifuge and determine the conductivity of the supernatant medium.

Green found that the conductivity of the dead suspension is considerably greater than the conductivity of the original medium. The conductivity of the supernatant medium taken from above the dead bacteria is considerably greater than that of the dead suspension. This increase in conductivity of the medium in which the bacteria have been killed is due to the fact that salts have diffused out of the dead bacteria—a fact which may be determined not only by electric conductivity but by quantitative analysis of the several salts which have diffused. That is to say, the chlorides, sulphates and phosphates of sodium, potassium, calcium and magnesium have diffused out. This shows that living bacteria may take up and store salts on the inside of them to a higher concentration than exists in the medium. The ability of living cells to do this is rather generally known, and is the basis of the kelp-potash and iodine industry, the kelp storing up potash to an enormously greater concentration than exists in the sea-water and concentrating iodine even more highly. In order to hold the salts inside at this high concentration some barrier to their exit must be set up.

Shearer worked on electric conductivity of bacteria but did not arrive at the same results as found by Green. Shearer was not able to determine any electric resistance due to bodies of dead bacteria. Whether this failure was due to the fact that the suspension was too dilute is not clear. As mentioned above even protein in solution offers an electrical resistance by increasing the viscosity, and dead bacteria contain some protein. The experiments of Shearer in regard to antagonistic effects of ions confirmed those of Osterhout, or rather extended Osterhout's experiments on sea-weed to bacteria. Shearer found some correlation between conductivity and virulence in the case of some pathogenic bacteria. The virulence decreased in the presence of monovalent salts (which had been shown to increase conductivity) and increased upon addition of a small trace of Ca. In general, he found that the resistance of the solution increased in proportion to the bacteria present (volume ratio). His experiments along this line, however, were not quantitative.

YEAST

Green, in conjunction with Johnson, studied the conductivity of yeast. They found that dead yeast cells raised the resistances of the media appreciably when suspended in them, but not to so great an extent as did the live cells. They point out that there are three factors concerned with the drop in resistance of a cellular suspension on death: exosmosis of salts, decrease in size of cells with a resultant decrease in ability to displace a better conducting medium, and increased conductance of the cells. Shrinkage in yeast cells upon death was greater than in bacterial cells, and hence was probably an appreciable factor in the decrease in resistance observed on heating the suspension. The magnitude of the resistance offered by the yeast cells was also dependent upon the strength of the electrolyte suspending them. When no change took place in the resistance of the medium on death of the cells, Johnson and Green interpreted their results to mean that the concentration of the menstruum probably represented the concentration of the diffusible salts inside the cell. If the concentration of salts outside of the cell differed from that inside, diffusion would occur on death of the cells in the direction of higher to lower concentration and hence cause a corresponding rise or fall in the resistance of the medium.

NERVE

The relation between electric conductivity and the rate of the nerve impulse was discovered by Mayor. Mayor found that certain nerve preparations that behaved normally in sea-water were affected by dilution of the sea-water in such a manner that the decrease of electrical conductivity of the sea-water was proportional to the decrease in the rate of the nerve impulse. This parallelism was not complete, however, as with all vital phenomena it holds only within certain temperatures. Some lack of parallelism is to be expected because very high temperatures or very low temperatures kill the nerve. The cause of the relation found by Mayor between electric conductivity of the medium and rate of the nerve impulse might be harmonized with R. S. Lillie's theory of nervous conduction as follows: The nerve may be stimulated by an electric current and when it is stimulated it sets up a little current within itself similar to the local action current due to scratching a passive iron wire. This local action current is transmitted by ions in the medium and stimulates an adjacent portion of the nerve. The greater the electric conductivity of the medium the more rapid the transmission of the local action current (in case of the passive iron wire), and hence the more rapid the spread of the stimulated area, or in other words, the more rapidly the nerve impulse is propagated.

THE PSYCHOGALVANIC REFLEX

It was shown by Gildemeister and his pupils that the electric resistance of the body is chiefly due to the resistance of the skin and is greater the lower the frequency of the alternating current, being greatest with direct current. This indicates that the resistance is due to membranes which become polarized by the current.

Moderate doses of anesthetics increased the resistance to currents of low frequency. The same action was produced by small amounts of the salts of rare earth metals. Lethal doses of anesthetics and powerful electric currents decreased the resistance.

It has been observed that if a person becomes mentally agitated, as on hearing bad news, the electric resistance of the body decreases. This is called the psychogalvanic reflex by psychologists and clinicians. Gildemeister (1915) showed that the decreased resistance is due to the activity of sweat glands. Schwartz (1915) showed that the electric resistance of frog's skin is decreased when the nerves of the skin are stimulated.

Ebbecke (1922) observed that the electric conductivity of living nerve tissue to direct current is increased around the cathode and decreased around the anode. If both electrodes are laid on the living nerve these effects counterbalance one another, but if the nerve is killed around one electrode, the effect of this electrode is abolished and the effect of the electrode on the living nerve is made evident.

OTHER EVIDENCE OF CHANGES IN PERMEABILITY

It was shown by Lillie that the pigmented cells of Arenicola larvæ lost their pigment into the surrounding water when they were stimulated and he interpreted this as an increase in permeability. Blood-cells lose their pigment when hemolyzed but they are killed in the process. Cells of red beet lose their pigment when stimulated but the degree of injury has never been determined. Lyon and Shackell showed that dyes penetrate fertilized sea urchin eggs more rapidly than unfertilized. The previously mentioned observations that the permeability of the sea urchin's egg increases when it is caused to develop was confirmed on the eggs of the frog and certain fish that lay their eggs in fresh water (McClendon). The frog's egg may be caused to develop by means of an electric shock and this process does not add any electrolytes to the water. Electrolytes, however, diffused out of the egg into the water, and were detected by chemical means, whereas they did not diffuse, at least not so rapidly, out of unstimulated eggs. This explains the results of Bachmann and Runnstrom who found that the osmotic pressure of frog's eggs greatly decreased on fertilization.

Tennent made observations from which he concludes that the spermatozoa of some Echinoderms cause greater increase in permeability of the eggs they fertilize than do spermatozoa of other species. Under ordinary conditions, cross-fertilization does not occur or does not lead to development of the egg. He was able to cross-fertilize successfully by treatment of the eggs with certain electrolytes. Osterhout has shown that some of these electrolytes increase permeability and others decrease permeability. Tennent assumes that this applies to Echinoderm eggs and explains the action in making cross-fertilization successful by assuming that the permeability change is the algebraic sum of the effects of spermatozoa and electrolytes and that the proper degree of permeability assures the success of cross-fertilization.

Richards and Packard observed that mild treatment with x-rays may cause increase in the permeability of cells, according to their interpretation.

Hamburger and Alous observed that removal of Ca from the perfusion fluid caused increase in permeability of the kidney for glucose. Ca could be substituted by Sr or Ba but not Mg.

Banus observed increase in permeability of the water-plant Spirogyra to sulfonic acid dyes during the passage of alternating or transient electric currents through the water. If after the stimulation the Spirogyra remained for a time in a solution of acid fuchsin or cyanol and was then transferred to pure water, the dye was trapped and could not get out of the cells unless stimulated again. Lund obtained microscopic evidence of change in the plasma membrane of the protozöon, Noctilucca, on electric stimulation.

ANESTHESIA

The power of anesthetics in restraining the activity of the central nervous system, especially the reflex and voluntary activities which they affect in lower concentrations than those affecting other organs, is well known. Since the higher animals die as soon as the activity of the respiratory center ceases, and under artificial respiration as soon as the heart-beat ceases, it is possible in the intact animal to study the effects of anesthetics only on certain nerve synapses—*i. e.*, structures whose threshold of anesthesia is lower than that of the heart mechanism. Anesthetics in higher concentrations suspend the activity of animals lacking a nervous system, as well as the movements of plants.

Overton (1901) observed that vertebrates, insects, and entomostraca (small crustacea) require almost the same concentration of anesthetic in order to suspend reflex excitability, whereas certain groups of worms require double this concentration. Protozoa and plants require, in order to suspend their activities, six times the concentration of anesthetic required to anesthetize vertebrates. From Warburg's data, the concentration of anesthetic necessary to reduce the oxidation of goose-erythrocytes 30 to 70 per cent. is about six times the concentration necessary to anesthetize vertebrates. It follows from this that protozoan and plant cells react to anesthetics, not like nerve synapses but like mammalian cells.

Höber first clearly stated a theory of anesthesia based on permeability. He expressed the idea that stimulation consists in an alteration of the state of the colloids of the plasma membrane in such a way that permeability is increased. Anesthetics act upon the colloids in such a way that this increase of permeability is prevented. Höber believes that the lipoids such as lecithin are the colloids affected and that narcosis is brought about by the solution of the anesthetic in the lecithin, resulting in a stabilizing of the colloid concerned in stimulation. Höber showed that an antagonism exists between certain anesthetics, such as ethyl and phenyl urethane, chloral hydrate, chloroform and hypnon on the one hand, and rubidium and potassium salts on the other, the latter causing negative variation in frog's muscle and the former preventing its appearance.

Lillie working with Arenicola, a marine annelid, observed that outward diffusion of a brown water-soluble pigment may occur under conditions of increased permeability as mentioned before, and that this diffusion failed to occur in the presence of certain anesthetics. He transferred the larvæ from sea-water to pure isotonic sodium chloride solution and obtained strong muscular contraction accompanied by a well marked loss of pigment. If, instead of pure sodium chloride, a little of the anesthetizing salt, magnesium chloride, was added, neither contraction nor loss of pigment occurred. Later, Lillie observed a similar occurrence in the case of Arbacia eggs, pure solutions of certain salts causing an outward diffusion of pigment and certain anesthetics added to the solutions preventing the diffusion. He interpreted these results as showing that anesthetics prevent the increase of permeability normally produced by certain salts such as sodium chloride.

S. Loewe (1913) observed that anesthetics decrease the electric conductivity of lipoid membranes soaked in salt solution. These results are probably due to increase in size of colloidal lipoid particles. Clowes (1916) supposes the plasma membrane to be an emulsion of lipoid in water that is changed by anesthetics to an emulsion of water in lipoid.

Osterhout (1913) observed that small quantities of anesthetics added to the sea-water decrease the electric conductivity of sea-weed, and Osterhout (1919), Gildemeister (1920) and Ebbecke (1921) found this true of skin. Since Na increases the conductivity it seems probable that the anesthetic in the sea-water inhibits the action of the Na already present.

Hemolysis consists in the loss of the hemoglobin from the red blood-corpuscles. Not only does the permeability to hemoglobin increase but as mentioned above Stewart (1899) has shown that the permeability to ions increases. Arrhenius and Bubonovic observed that anesthetics inhibit hemolysis by hypotonic solutions. Joel (1915) showed that anesthetics inhibit the permeability-increasing action of pure cane-sugar solution on erythrocytes.

The eggs of certain fish are admirable for permeability studies, since they develop in distilled water, in which they neither swell nor lose salts. It had been observed that the permeability of Fundulus eggs may be increased by certain solutions of salts, alkaloids or other substances in concentrations that do not kill them (McClendon, 1912–1913). The eggs of the pike behave similarly. These eggs are impermeable to water or to salts, but when placed in 0.1 M $NaNO_3$ solution they lose chlorides, which pass out into the nitrate solution and may be estimated with Richards' nephelometer. Three per cent. ethyl alcohol causes retardation in the development of these eggs and is therefore considered an anesthetic. If the eggs are placed in 0.1 M $NaNO_3$ solution containing 3 per cent. alcohol, only half the amount of chlorides diffuse out of them as when placed in pure 0.1 M $NaNO_3$ solution. The anesthetic inhibits the permeability-increasing action of the pure salt solution (McClendon, 1914, 1915).

The skin current of the frog disappears when the skin is anesthetized, indicating that the hypothetic increase in permeability of the outer surfaces of the gland cells during secretion may be inhibited by anesthetics.

It seems clear, therefore, that anesthetics inhibit the increase in permeability of the plasma membranes of the irritable elements. In order for them to do this it is necessary for them to penetrate only the surface film of the cell. But anesthetics belong to the group of substances which penetrate cells easily, and the question arises as to their effect on the interior. Some experiments on catalysis are suggestive. If blood charcoal is mixed with a solution of oxalic acid containing atmospheric oxygen, the acid is burned to CO_2 and H_2O. Blood charcoal contains mineral matter, including iron, which is not entirely removed by extraction with HCl and we cannot say that it is the carbon that acts as the catalyzer. Warburg found that the catalytic power of charcoal varies with its power of adsorbing oxalic acid, hence the combustion probably takes place on the surface of the charcoal. He observed further that anesthetics (of the urethane series) inhibit the oxidation and explained this as due to the displacement of the oxalic acid from the surface of the charcoal by the anesthetic (which is adsorbed to a greater extent than the acid). McClendon confirmed these results, using charcoal extracted with concentrated HCl followed by H_2O for many hours. This charcoal was heated to redness and cooled in a CO_2-free atmosphere. When placed in oxalic acid solution the charcoal adsorbed all of the CO_2 produced for a time, but after it had become saturated with this gas, the volume of O_2 used up was half the volume of the CO_2 given out. Amino acids may be burned in this way.

Meyerhof (1914) observed that the catalysis of hydrogen peroxide by colloidal platinum may be inhibited by anesthetics. Since the anesthetic did not reduce the number of particles of platinum seen in the ultramicroscope he concluded that it did not cause aggregation but that the anesthetic displaced the H_2O_2 from the surface of the platinum.

Meyerhof (1915) showed that the action of invertase from yeast may be inhibited by anesthetics. The following table shows the concentration of anesthetic that reduced the inversion of 3 per cent. cane-sugar solution 30 per cent.:

Methyl alcohol	3.0 *M*
Ethyl alcohol	1.3 "
Propyl alcohol	0.5 "
Isobutyl alcohol	0.27 "
Isoamyl (fermentation)	0.21 "
Methyl urethane	0.95 "
Ethyl urethane	0.97 "
Propyl urethane	0.48 "

In this case the Tyndall phenomenon was increased, but this may have been due to the films of anesthetic on the invertase particles rather than to an aggregation of the particles. In harmony with the view that the reduction in activity of the enzyme is due to the displacement, by the anesthetic, of the sugar from its surface, is the fact that if the concentration of the anesthetic is varied its effectiveness follows the typical adsorption isotherm. The concentration of anesthetic necessary to anesthetize tadpoles reduced the inversion about 20 per cent.

If the anesthetics are added in greater concentrations to enzyme-containing extracts of cells, precipitation may occur. The enzymes are carried down in the precipitates, but it is not clear whether the enzyme is precipitated directly by the anesthetic, or protein impurities precipitated and the enzyme adsorbed by the protein. Battelli and Stern (1913) showed that anesthetics precipitate nucleoprotein.

Warburg and Wiesel (1912) observed that anesthetics inhibit the fermentation by yeast juice, attributing this inhibition to the precipitation of the zymase, since the inhibiting and precipitating powers of anesthetics are parallel. However, live yeast requires for inhibition less concentration of anesthetic than is required by yeast juice (or for precipitation of protein).

Vernon (1912) observed that anesthetics are harmless to the indophenol-oxidase of chopped kidney until a certain concentration is reached, above which they inhibit its action. The data of Batelli and Stern are given in the following table, as compared with the anesthesia of tadpoles by Overton and the reduction of the respiration of sea urchin eggs, fish sperm, goose erythrocytes, lymphocytes, liver cells, spinal cord, yeast and bacteria 30 to 70 per cent., by Warburg. The figures are the gram molecular concentrations:

	Inhibition of oxidation at 15°. ?	Precipitation of nucleoproteid (Battelli and Stern).	Anesthesia of tadpoles (Overton).	Inhibition of respiration of cells (Warburg).
Methyl alcohol	11.44	12.48	0.62	5
Ethyl alcohol	6.12	6.97	0.31	1.6
Propyl alcohol	2.04	2.72	0.11	0.8
Isobutyl alcohol	1.06	no ppt.	0.045	0.15
Iso-amyl alcohol	0.41	no ppt.	0.023	0.045
Acetone	5.70	4.34	0.26	
Methylethylketone	2.22	2.41	0.09	
Methylpropylketone	0.77	no ppt.	0.019	
Allyl alcohol	2.70	4.05		
Ethyl urethane	1.90	2.58	0.037	0.33

This table shows that about six times the concentration of anesthetic effective on tadpoles is required to inhibit the respiration of goose erythrocytes. Gros (1910) found the same thing true for the anesthesia of peripheral nerves. It seems, therefore, that the nerve cells of the tadpoles are not anesthetized, but the synapses are reduced to the same condition as during sleep. For anesthesia of nerve cells and reduction of the respiration of goose erythrocytes the same concentration is required, but for inhibition of the oxidases and precipitation of protein in Batelli and Stern's experiments more than double this concentration is needed. In fact, the concentration used by Batelli and Stern is much above the lethal dose for cells. Warburg (1911) explains the fact that anesthetics inhibit enzymes, when contained in living cells, in lower concentrations than the same anesthetics inhibit the same enzymes in cell extracts, by the assumption that the enzymes within the cells are adsorbed to phase boundaries, the anesthetics becoming more concentrated at the phase boundaries. If this explanation is correct we must make the further assumption that the enzymes in the cell extracts of Warburg are in true solution, whereas the invertase used by Meyerhof formed a colloidal solution because the invertase was inhibited by as low a concentration of anesthetic as is required to inhibit the respiration of the erythrocytes.

Various other processes concerned with internal activities of cells have been reported as affected by anesthetics. These include such changes as occur in response to electrical and chemical stimuli, protoplasmic rotation and absorption of carbon-dioxide

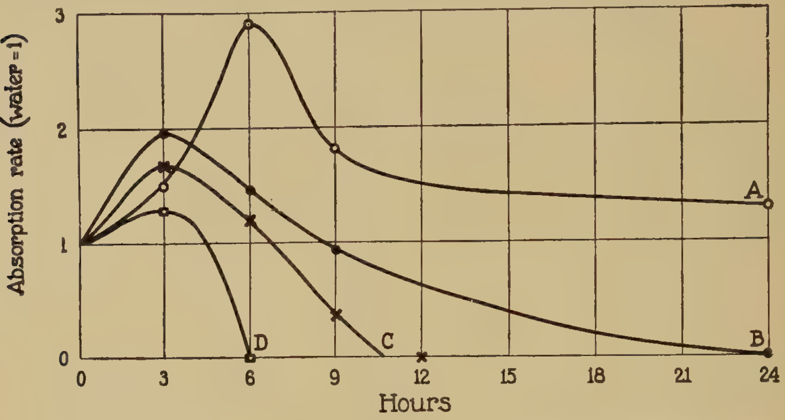

Fig. 30.—Relative rate of O_2 absorption of elodea in solutions of ether in darkness. Curve A, 1.5 per cent. ether; B, 3 per cent.; C, 5 per cent., and D, 8 per cent. (From Journal of Biological Chemistry.)

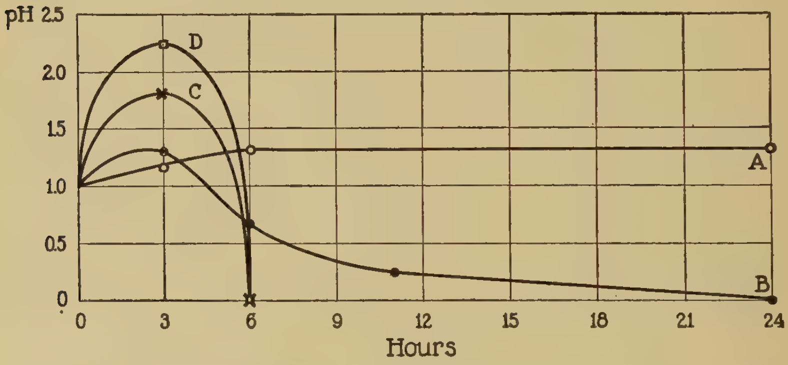

Fig. 31.—Relative change of pH (due to CO_2 production by elodea) in solutions of ether in darkness. Curve A, 1.5 per cent. ether; B, 3 per cent.; C, 5 per cent.; D, 8 per cent. (From Journal of Biological Chemistry.)

in plants, cell-division, artificial parthenogenesis in unfertilized eggs and even growth in plants and animals. Medes and McClendon tested the effects of various anesthetics on a number of the activities of Elodea, such as oxygen consumption and carbon dioxide elimination (in the dark), photosynthesis, exosmosis of chlorides and rate of protoplasmic rotation (Figs. 30-34). They found that any given concentration of the anesthetic might affect

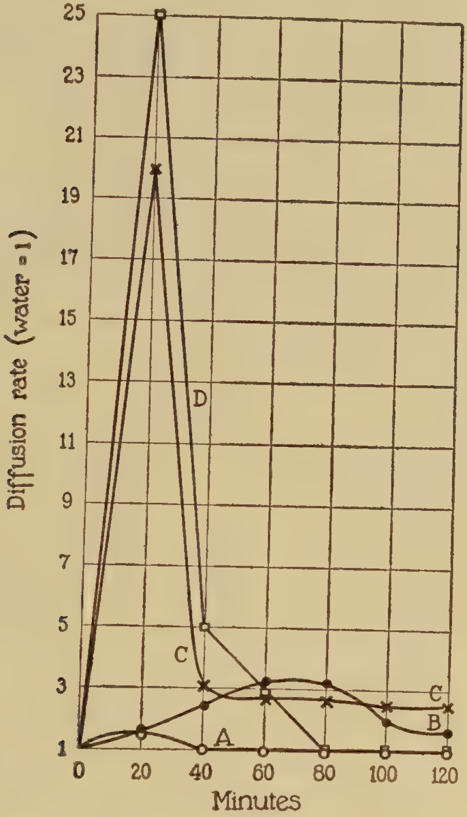

Fig. 32.—Diffusion of chlorids from elodea in solutions of ether. Curve A, 1.5 per cent. ether; B, 3 per cent.; C, 5 per cent.; D, 8 per cent. (From Journal of Biological Chemistry.)

the various activities to different extents, in some cases even increasing some activities at the same time that others were depressed. Although other interpretations are possible, this would seem to indicate that anesthetics affect the phase boundaries between or within the cells and thus modify processes going on at these boundaries. The fact that some process could be stopped while others continued would also seem to indicate this.

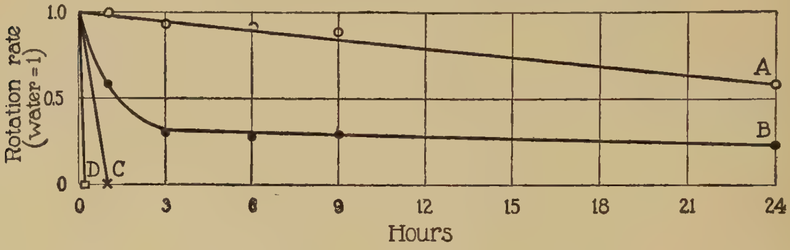

Fig. 33.—Rate of protoplasmic rotation in elodea in solutions of ether. Curve A, 1.5 per cent. ether; B, 3 per cent.; C, 5 per cent.; D, 8 per cent. (From Journal of Biological Chemistry.)

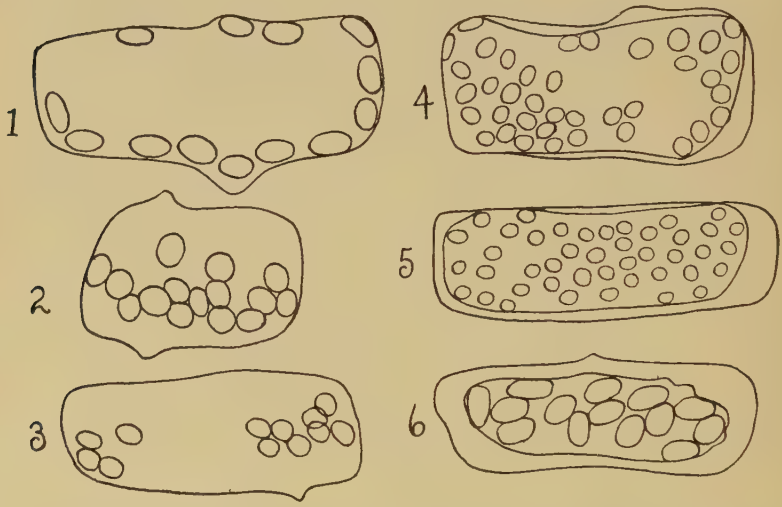

Fig. 34.—Camera lucida drawing of elodea cells: 1, Normal cell; 2, cell exposed two hours to 1.5 per cent. ether; 3, cell exposed two hours to 3 per cent. ether; 4, cell exposed two hours to 5 per cent. ether; 5, cell exposed two hours to 8 per cent. ether; 6, cell exposed twenty-four hours to 0.1 per cent. chloretone. (From Journal of Biological Chemistry.)

Although Battelli and Stern maintain that anesthetics precipitate proteins Traube and Köhler (1915) and Traube (1915) assert that anesthetics help in the solution of proteins. Traube had pointed out the relation of adsorption to anesthetic action. Kochmann observed that anesthetics shrink proteins. In the following table are arranged anesthetics according to their power of hastening the swelling and peptization of gelatine jelly (and retarding gelation of sols). It is found that with few exceptions they are in the order of anesthetic power, as shown by the figures in the last column, which represent the molecular concentration for anesthesia.

Anesthetic.	Anesthetic concentration (Overton).
Phenanthren	0.0000037 *M*
Thymol	0.000055
Naphthalene	0.000065
Chloroform	0.0014
Chloral hydrate (acid)	0.006
Ethyl ether	0.001
Ethyl chloride	0.0045
Sulfonal	0.0088
Trional	0.0064
Iso-amyl alcohol	0.023
Ethyl urethane	0.041
Isobutyl alcohol	0.045
Methylethyl ketone	0.09
Ethyl acetate (acid)	0.03
Tert. amyl alcohol	0.057
Propyl alcohol	0.11
Acetone	0.26
Ethyl alcohol	0.39
Methyl alcohol	0.57

Perhaps the anesthetics protect the gelatine from the precipitating action of accidental impurities. On the contrary, if impurities hold a protein in solution the anesthetic might then help precipitate the protein. This may explain the opposite effect of anesthetics on nucleoprotein solutions.

This action of anesthetics in displacing other substances from the surface film probably explains the observation of Abl (1907) that they reduce the electrolytic solution tension of cadmium, and the observation of Grumbach (1911) that they reduce the contact potential between dielectric and electrolyte.

The action of anesthetics on living cells may be explained by the same assumption—*i. e.*, that they cover the plasma membrane with a film that protects it from change, entering the cell and displacing enzymes or reacting substances from the phase boundaries where these reactions occur more rapidly than elsewhere. The synapses that have to do with consciousness are more sensitive to anesthetics than are either plasma membranes or these enzyme reactions. Anesthesia requires only one-sixth the concentration that is required to inhibit cell activities in general.

This hypothesis also explains the relation between anesthetic power and surface tension. The generalization that the more an anesthetic lowers the surface tension of water the greater is its anesthetic power is nearly correct, because of the fact that anesthetics that lower the water-air surface tension are adsorbed to many water-solid or water-liquid surfaces.

According to Overton (1901), anesthetic power varies with the partition-coefficient of the anesthetic between lipoid and water. This partition-coefficient has never been determined, but these authors have been content with the partition-coefficient between olive oil and water or between some solution of lipoid and water. In many cases even this was not determined, but the ratio between the solubility in lipoid solution and in water was substituted. It seems generally true that substances that lower the surface tension between water and air very greatly, have a partition-coefficient in favor of oil and are therefore soluble in oil—they are also soluble in many other organic solvents. The solubility of an anesthetic in lipoid solutions seems to be due to the fact that it is adsorbed by the colloidal particles of lipoid so that the solution can hold more anesthetic than the solvent (benzene, etc.) can. Thus adsorption appears to be the basis of the whole matter.

In some cases the partition-coefficient of the anesthetic between cells or tissues and water has been determined. Warburg, by this means, concluded that the erythrocytes consist of a larger volume of watery phase than of lipoid phase.

It has been shown by a number of investigators that alcohol, ether, chloroform, chloral hydrate and acetone become more concentrated in nerve than in other tissue, this being used to explain the ease with which the central nervous system may be anesthetized. The nervous system, however, stores the anesthetic partly in lipoids which are more abundant in the white matter forming the myelin sheaths of the nerves. The nerve fibers are no more easily anesthetized than non-nervous cells (Gros). Nerve impulses are still transmitted in the anesthetized body, only certain nervous processes being stopped, as in sleep. This stoppage may be explained by the assumption that certain synapses are affected by the anesthetic.

Many anesthetics, even in the optimum concentration, have not only an anesthetic but also a toxic action, so that prolonged anesthesia is harmful. This is characteristic of all anesthetics with acidic or basic properties—the alkaloids, for instance, whose chemical affinity may explain their selective action on certain cell structures. Other anesthetics are decomposed in the body into harmful substances. Esters are hydrolyzed with the liberation of acids.

But even the purest types of anesthetics are toxic if the anesthetizing dose is exceeded. This toxic action is manifested by increase in permeability, which is reversible only if very slight and momentary.

When ether is given to an animal, a stage of excitement sometimes precedes that of narcosis. Hamburger (1912) observed that ameboid motion is increased by minute doses of anesthetics. Johannsen (1906) observed that lilacs sprout earlier after treatment with ether vapor. Medes and McClendon observed that the respiration of a plant, elodea, is increased by anesthetics. Further examples of the stimulating action of anesthetics are given by Carlson (1906), Vernon (1912), Tashiro and Adams (1914), Lee (1903), and Lee and Salant (1902).

The table on page 346 (modified from Lillie, 1916) summarizes the effect of anesthetic alcohols on various processes, giving the effective molal concentrations.

Effect.	Methyl.	Ethyl.	Propyl.	Butyl.	i-Amyl.
Narcosis of tadpoles (Overton)....	0.57	0.29	0.11	0.038	0.023
Phototropism of Daphnia (Loeb)..	0.6	0.2	0.075	0.04	
Inhibition of sea urchin eggs (Führer).....................	0.72	0.41	0.136	0.045	
Retardation of fish eggs (McClendon).....................	....	0.52	....	....	0.015
Half rate of turtle ventricle (Vernon).........................	1.1	0.53	0.23	0.05	0.02
Narcosis of Daphnia (Loeb)......	1.2	0.6	0.2	0.12	0.04
Inhibition of sea urchin eggs (Lillie)......................	.....	0.87	0.27	0.086	0.037
Narcosis of worm larvæ (Lillie)...	2.2	1.1	0.34	0.09	0.03
Depression of invertase (Meyerhof)	3.0	1.3	0.5	0.27	0.21
Half oxidation in erythrocytes (Warburg)..................	5.0	1.6	0.8	0.15	0.045
Ppt. nucleoproteid (Bartelli and Stern)......................	5.7	2.38	1.12	0.45	0.21
Inhibition of ether-yeast (Warburg).......................	5.0	3.5	1.3	0.54	0.23
Kills muscle oxidon (Bartelli and Stern)......................	7.54	3.57	1.16	0.44	0.19
Kills indophenol oxidase (Vernon).	12.0	6.4	3.1	0.61	
Reduce surface tension to 0.5.....	14.0	5.0	1.6	0.46	0.14

BIOELECTRIC PHENOMENA

It was observed by DuBois-Reymond (1848) that when a nerve or muscle is cut across and electrodes applied, one to the cut end and the other to the uncut surface, the so-called current of injury, whereas variable, is often about 0.06 volt. In order to explain this phenomenon this investigator postulated a polarity of the tissue, that is to say, he supposed that it was made up of molecules electropositive on one end and electronegative on the other end, and the electropositive ends were all turned toward the outside of the muscle so that by cutting it you could apply one electrode to the electronegative end, the other being applied to the electropositive surface of the muscle. (Such an explanation is given for the structure of fixed magnets except for the fact that the whole molecule is not supposed to be the elementary magnet, but the latter is supposed to be an electron orbit inside the atom and is called a magneton.) There is nothing at all preposterous in this view; in fact, this polarity is emphasized nowadays and molecules are divided into polar molecules and non-polar molecules, the cause of polarity being a local unbalancing of electric charges. But, in order that the living tissue may do work on the galvanometer, some decrease in the energy of the tissue must occur. Living tissue is, moreover, not all solid and the interior of many cells has been shown to be in a liquid condition. The polarized layer is therefore best represented as the surface layer of the cell.

Wilhelm Ostwald (1890) proposed the membrane theory of the bioelectric currents. This membrane was supposed to be permeable to cations and not to anions. Bernstein (1902) suggested that the ions passing the membrane and giving rise to the electric current were potassium ions, but Höber (1905) supposed that some other ion was concerned. Cremer made a model designed to represent the bioelectric current, by placing a little nitrobenzene in the bottom of a U-tube and dissolving picric acid in the nitrobenzene in one arm only, then filling up the two arms of the U-tube with sodium chloride solution. This arrangement gave rise to an electromotive force. Brünings (1907) placed a copper sulphate solution in contact with a potassium ferrocyanide solution, which caused a precipitate of copper ferrocyanide at the junction. The osmotic concentration of the two solutions was the same. An electromotive force of about one-tenth volt was produced and was almost independent of the concentrations of the solutions from 0.005 to 0.5 M. Haber (1908) made a membrane or intermediate phase out of a non-aqueous medium and placed on each side of it the same electrolyte, the concentration of the electrolyte being different on the two sides. He found that the electromotive force was that approximately calculated from Nernst's formula, supposing the speed of passage of one of the two ions of the electrolyte was zero in the non-aqueous phase, but that the other ion passed through.

$$E = \frac{u - v}{u + v} \frac{RT}{96500} \log_e \frac{c_2}{c_1}$$

Beutner has done the most extensive work on this type of membrane and has collected it in book form (1920). Beutner set up many membranes of weakly polar solvents immiscible with water. By choosing this non-aqueous phase he could set up a system permeable only to one ion and have that either the cation or the anion. According to Beutner the ion combined by means of a free valence bond with the solvent at one side of the membrane and dissociated at the other side, passing through the membrane in the form of a neutral molecule. In order for a continuous current to pass, however, it is necessary that either free electrons or ions pass *through* the membrane. Of course, it is possible that an ion of the opposite sign passed in the opposite direction and this ion might never leave the membrane but on passing through, might unite with an ion of the water phase and go back with it carrying it through the membrane as a neutral molecule.

It is supposed by Mathews (1924) that the current goes through the cell membrane in the form of electrons that pass from carbon atom to carbon atom of the carbon chain of organic molecules. He supposes that the carbon chain would be a conductor of the first class, similar to graphite. Such a membrane would be similar to that of a metallic membrane. For instance, if a copper membrane separates two water solutions of copper sulphate and the concentration of copper ions on one side is ten times as great as that on the other side, this ion will plate out on the membrane on the concentrated side and new ones form on the dilute side. The electromotive force will be about 60 millivolts depending on the temperature. Copper does not pass through the membrane but the current is carried through the membrane in the form of free electrons. The copper that dissolves off of the dilute side gives up electrons to the metal and these electrons pass through the membrane and unite with copper ions on the other side reducing them to metallic copper. If the membrane is thin the copper that plates on one side will finally dissolve at the other and copper pass through the membrane. If a living cell were surrounded by such a membrane the outside of the cell would be oxidized and the inside of the membrane reduced by the passage of the polarizing current. Mathews supposes that the oxidation-reduction potentials on the outside and inside of the membrane are responsible for the bioelectric current.

All of these models of a membrane except that of Cremer represent the membrane as a simple partition or phase. It is probable that the copper ferrocyanide membrane is simply a solid partition with such small holes in it that only the potassium ions can pass through. The question of the passage of substances through membranes composed of organic solvents is involved in the theory of solubility in such solvents. It would take us too far afield to go into the question of solubility here. The membrane of Cremer is a double membrane and it seems probable that we should consider the seat of the electromotive force the boundary between the two halves of the membrane—in other words, that this is a liquid junction between two organic liquids. It is possible to produce considerable electromotive force by means of a liquid junction between water solutions. If we set up the concentration chain:

$$Hg, Hg_2Cl_2, KCl, 0.1N\ HCl, N\ HCl, KCl, Hg_2Cl_2, Hg,$$

an electromotive force is produced of about 40 millivolts, the dilute side of HCl being electropositive.

Planck has designed a formula for the calculation of this boundary assuming a sharp boundary between the two HCl solutions. Henderson proposed another formula supposing there to be a gradual gradation of concentration, and G. N. Lewis has adopted an empiric formula giving an intermediate value (see section on Hydrogen Electrodes, Chapter IV). Owing to the mixing of the two solutions, the electromotive force is not constant; it is high at first, and gradually disappears. The same would be true of the concentration chain in non-aqueous solvents such as used by Cremer. Beutner, on the basis of experiments on the skin of a healthy apple, supposes bioelectric phenomena, at any rate the current of injury, to be due to such a concentration chain. He found that a cut piece of the apple showed electromotive force when led off from the cut surface and the uncut by identical solutions, but when he scraped out the pulp of the apple and scraped the inside of the skin, the current disappeared. He assumed that he was scraping away an oily layer. It would seem more probable, however, that the apple skin acted like the thin glass membrane used by Haber and Klemensiewicz. If the hydrogen-ion concentrations on the two sides of this glass membrane are different, the membrane behaves as though it permits the passage of hydrogen ions but not the anions of the acid. It is possible that the apple skin allows passage of the hydrogen ions of malic acid and not of the anions, and the scraping removed a colloidal gel containing an aqueous solution of malic acid. If the pulp of the apple is not scraped away the electromotive force is maintained for a long time.

In making a model of the plasma membrane of the living cell it is desirable to have the electrolyte responsible for the electromotive force of such a nature and concentration that it may exist in the living tissue. Fahr favored the view that K^+ is the ion concerned. Hydrogen ions, being so very rapid in diffusion and so small that they might easily pass through membranes, seem very likely to be the ions concerned, especially as the outside of the cell is electropositive to the inside and acids (carbonic and lactic) are produced inside the cell because of the metabolism of the cell. The hydrogen-ion concentration on the outside of many cells in the body corresponds to a pH of about 7.45 (the blood plasma being 7.45). In order to produce an electromotive force of about 60 millivolts it would be necessary to have the hydrogen ion concentration on the inside of the cell correspond to a pH of about 6.45. The acidity of this solution is then less than that of ordinary distilled water exposed to the CO_2 of the atmosphere. The pressed juice of many tissues is more acid than this. Therefore it seems possible that the difference in concentration of hydrogen ions inside and outside of the cell is sufficient to give rise to an electromotive force of about 60 millivolts. This is approximately the electromotive force that is usually observed in the so-called current of injury by which the difference in potential on the cut and uncut surfaces, that is, inside and outside of the cell, is measured. Therefore, a model was set up containing a membrane of benzene. Buffer solutions were placed on the two sides of the membrane, one having a *p*H of about 7 to represent the outside of the cell, and the other of about 6 to represent the inside of the cell. An electromotive force of 31 millivolts was observed (McClendon, 1917). The low value may have been due to leakage since the benzene membrane was very thick and its permeability to hydrogen ions very low.

The so-called action current is similar to the current of injury except that it is transitory. The stimulated portion of a cell becomes electronegative similar to the cut or injured portion in the previous discussion. This electronegativity is transmitted to the other portions of the cell. In a fraction of a second the electropositivity of the cell surface is regained, the portion that was negative first regaining its positivity first. In some plant cells the time elements are longer and may be several minutes. These action currents were studied a great deal by Burdon-Sanderson and later by Waller. Waller showed that the electric conductivity of the plant tissue increased during the presence of the action current (blaze current).

The current of action may then be considered a temporary injury. It appears as though the membrane were temporarily removed and then regenerated. The complete removal of the membrane substances at any point would not seem to be necessary, however, since a copper ferrocyanide membrane may change as to permeability and if we have a drop covered entirely over with a copper ferrocyanide membrane it seems probable that we should get an electric current by increasing the permeability of the membrane at one point.

Lillie has shown that models of the action current of the nerve may be made by using wires on which metallic films represent the membrane and the removal of the film causes the action current. In the first place, it should be remembered that the nerve fiber is a portion of a very elongated cell, and in an elongated structure like this, the process of propagation can be studied more readily than in the case of a spherical body. If a metallic wire is placed in an oxidizing solution, an oxide film is formed on the surface. When the bright wire is first immersed in the solution an electric double-layer is formed, the potential of which can be calculated from the electrolytic solution tension of the metal and the concentration of the metallic ions in the solution. The surface of the oxide film may also represent an electric double layer but the potential difference between oxide and solution at the one end and that between metal and the solution at the other are different. It was found by Lillie that if the wire coated with the oxide film is scratched at one point and electrical connection made between the scratched and the unscratched portions an electric potential difference can be observed. Furthermore, the oxide film dissolves off at the edges of the scratched area, thus laying bare a larger amount of the bright metal. This area spreads. The spreading action simulates the transmission of the nerve impulse. Thus Lillie has shown that if an iron wire is immersed in dilute nitric acid, allowed to remain until the iron oxide film forms (passive iron) and then is scratched at one end, the break in the oxide is transmitted without decrement to the other end of the wire regardless of its length. The eating away of the oxide film from passive iron might be represented in the nerve fiber by the dissolution of a layer one molecule thick on the surface, which when present would prevent the exit of anions. Hence the dissolution would be accompanied by a region of negativity.

It is easy to see how the oxide may re-form on the iron wire but the regeneration of the film on the nerve fiber is not so easy to picture. If it is a process of adsorption it is hard to imagine conditions that would alternately cause the molecules to be adsorbed and then be released. The process might be pictured in another way. Suppose the surface of the nerve fiber consists of a layer of colloidal particles so close together that only hydrogen ions can pass between them. If these particles are charged negatively they will repel anions and thus tend to make the membrane impermeable to anions. Hydrogen ions might diffuse through the pores so rapidly as to escape being bound by the membrane or there might be an equilibrium between the binding of hydrogen ions and of hydroxyl ions, the membrane retaining a certain dynamic negativity. If now a cathode is suddenly brought near one point of the membrane the equilibrium might be so disturbed as to produce some rearrangement of the particles, which would cause some of the pores to widen. This action of the cathode would be propagated. But after the disturbance is over the membrane regains its former condition and the mechanism of this has not even been suggested. Energy would be dissipated, however, by the escape of anions following the disturbance in the membrane. These anions would have to be restored by the formation and dissociation of more of the electrolytes concerned, before the original condition could be reproduced. In other words, metabolism would maintain the irritability of the nerve.

If the stimulation of the nerve is the bringing of a cathode near it, in other words, the accumulation of negative ions, the stimulus, i (stimulating current), would be a function of the current density and the time it flowed. Nernst proposed the formula:

$$i = I\sqrt{t}$$

where I is the current and t the time, and this has been found to be nearly true for durations of current from 0.0002 sec. to 0.001 sec. Lund has recently verified this formula by measuring the current necessary to stimulate a single cell, the protozoön, Noctilucca (personal communication).

According to the all or none law a nerve fiber is either stimulated maximally or no stimulus is propagated. Subminimal electric currents may change the quantity of additional current required to cause stimulation, but they have no effect on the other end of the nerve. The nerve impulse starts with a fixed value and is propagated without decrement under normal conditions. Since a nerve is a bundle of nerve fibers, quantitative differences in stimulation may be obtained by stimulating varying numbers of the fibers. Some may be more favorably placed than others to be affected by minimal stimuli. This may be the explanation of the fact that strong stimuli produce greater sensation than weak stimuli. Weber expressed this in an equation (Weber's law):

$$\delta s = \mathrm{k}\,\frac{\delta i}{i}$$

where i is the stimulus and s the sensation. If this is put into the form of a differential,

$$ds = \mathrm{k}\,\frac{di}{i}$$

it may be integrated similar to equation 4, Chapter II:

$$s = \int ds = \mathrm{k}\log_e i + \mathrm{c}$$

and is known as Fechner's law.

The Weber-Fechner law holds for medium stimuli.

The electric variation of the beating heart (electrocardiogram) is complicated by the anatomic arrangement of the conducting and contractile elements, but has been thoroughly analyzed by Einthoven and Fahr. Einthoven considers the so-called latent period between stimulation and response to represent the lag inherent in the apparatus for recording the results. By means of the string galvanometer the lag can be decreased.

The electric response of the retina to light is very complicated. Chaffee, Bovie and Hampson consider the time required for the maximum response to be different for the rods and cones.

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CHAPTER XIV

SURFACE FORCES

Two of the substances in the body most markedly affecting surface tension are the taurocholates and glycocholates of the bile. Soaps are also very surface-active, but it is doubtful to what extent they occur in the body. The free fatty acids also show activity in this respect but the higher fatty acids are so slightly soluble as to have very little effect in pure solution. The following table gives the surface tension of 0.25 *M* solutions at 15°. It will be noticed that sugars and amino acids raise the surface tension, urea is inactive, trihydric alcohols and amides lower it slightly, and monohydric alcohols, ketones, nitriles, organic acids and their esters lower it very much. In a series of compounds the effect is greater the longer the carbon chain.

0.25 molal.	s. t. $\left(\frac{\gamma}{\gamma H_2O}\right)$ at 15°.
Cane sugar	1.007
Glucose	1.004
Mannite	
Glycocoll	1.003
Water	1
Urea	1
Glycerol	.998
Glycol	.99
Acetamid	.986
Methyl alcohol	.966
Acetic acid	.961
Aceto nitrile	.95
Ethyl alcohol	.92
Acetone	.88
Ethyl urethane	.87
Propionitrile	.842
Propionic acid	.83
Methyl acetate	.83
Propyl alcohol	.8
Methyl ethyl ketone	.797
Diethylamine	.75
Piperidine	.738
Ethyl ether	.73
Pyridine	.73
Paraldehyde	.7
Chloral hydrate	.695
Butyric acid	.67
Isobutyl alcohol	.61
Tert. amyl alcohol	.60
Ethyl acetate	.58–.688
Iso-amyl alcohol	.42

Strong electrolytes change the surface tension only a very little according to the additive effects of the anions and the cations. Some hydrophile colloids lower the surface tension. In such cases they usually form haptogen membranes which are so solid that the surface tension cannot readily be measured. For instance, if a greased needle is floated on the surface of water, it bends the surface down and is held up by the surface tension. If the needle has been previously magnetized it will point North very readily no matter in what position it is first placed. If, however, a little saponin has been added to the water the needle remains fixed in whatever position it is laid, the haptogen membrane preventing its movement. Milk globules are covered with haptogen membranes. These are not casein. Their composition has recently been studied by Palmer and Samuelsson.

The surface tension of urine is ordinarily much lower than that of pure water. The substance responsible for this lowering is not known though it seems probable that traces of bile salts might be responsible. If bile salts are present in urine in sufficient amounts to be detected by Pettenkofer's reaction, they very greatly reduce the surface tension of urine. If flowers of sulphur are placed on such urine the particles sink because the surface tension is not strong enough to hold them up. G. D. Allen (1916) attempted to use the surface tension method as a quantitative test for the bile salts in the urine but since the effect of the bile salts is influenced by the simultaneous presence of other substances it was necessary to have more or less uniform conditions. For instance, NaCl and H ions increase the effect and OH ions decrease the effect. Therefore, the urine was diluted to a specific gravity of 1.01. In the following table the surface tension of the urine is given in percentages of that of distilled water at the same temperature.

S. T. of sample diluted to 1.010 specific gravity $\frac{\gamma}{\gamma_{H_2O}} \times 100.$	Minimum of sodium glycocholate which may give observed S. T. (Sample is acid.) Diluted sample. Gm. per 100 cc.	Maximum of sodium glycocholate which may give observed S. T. (Sample is alkaline.) Diluted sample. Gm. per 100 cc.
95	0	0.001
90	0	0.004
85	0.001	0.008
80	0.003	0.015
75	0.007	0.03
70	0.015	0.065
65	0.033	0.1+
60	0.1+	0.1+

The surface tension of blood-serum is considerably lower than that of water. Blood-serum is sometimes loaded with fat to such an extent that it appears milky. It may also at times contain sufficient bile to cause it to appear almost black. Since fatty acids and bile salts greatly lower the surface tension of water, one would expect great variations in the surface tension of the blood-serum; but as such surface-acting substances are very readily adsorbed, the large colloid content of the blood-serum makes the relations rather complicated. The surface tension of serum under certain conditions has been made the basis of the meiostagmin test for syphilis. There has been a great deal of dispute about the validity of this test and it has never competed very strongly with the Wassermann test.

ADSORPTION

Since all substances that lower the surface tension are adsorbed, adsorption must play a considerable rôle in living organisms. Whereas it is very simple to form an experiment *in vitro* to measure adsorption, the extent of adsorption in living matter is rather difficult to determine since the adsorbents are themselves unstable and of unknown composition and it is impossible to remove the adsorbed substance in order to measure its quantity or identify it without the possible danger of dissolving the adsorbent.

Adsorption is the chief basis of dyeing textiles and staining of histologic preparations of cells. The term adsorption is applied no matter what the forces are that cause the union of adsorbent and the substance that is adsorbed. In the case of the union of dyes with protein, since the basic dyes stain in alkaline solution and the acid dyes in acid solution, it seems probable that chemical reactions are involved. It is true, however, that substances that lower the surface tension of the water-air surface are adsorbed generally, and hence surface tension often plays a rôle.

Adsorption plays a prominent rôle in soils. Clay, aluminum hydroxide and ferric hydroxide are usually electropositive and adsorb anions. Kaolin, silica and charcoal are electronegative and adsorb cations. It is possible that in this way potash is held in the soil, although the greater proportion in many soils is in the form of orthoclase.

OXIDATION

As discussed in Part I, Clark has treated oxidation and reduction as electron pressure, but in many cases the electron pressure is not known.

Since many chemical reactions are known to be consummated by light rays and since it seems possible that radiant energy plays a part in oxidations that takes place at high temperatures, it is sometimes supposed that combustion at low temperatures is accomplished by other means. Wherever there is an oxidation there is a reduction. Hence it is possible that the concentration of free electrons in a solution determines the oxidation potential and that the process of oxidation is merely the attaining of an equilibrium, some substances being oxidized and others reduced until all are brought to this oxidation potential. As many hydrolyses are speeded up by enzymes extracted from living cells numerous attempts have been made to isolate oxidizing enzymes or so-called oxidases. Many peroxides exist in living cells and they favor oxidations in that they, themselves, are capable of reduction. Linseed oil oxidizes spontaneously in atmospheric oxygen, but the speed is almost imperceptible in the absence of light or of the peroxides of heavy metals such as ferric oxide. Ferric oxide is necessary for the spontaneous oxidation of lecithin in the dark. Tyrosinase and other special oxidases have been extracted from living cells but no oxidase that will accomplish the oxidation of glucose or lactic acid has been found.

Oxyhemoglobin is itself an oxide and is capable of oxidizing many substances without the addition of any catalyst. It has been shown by Warburg and others that activated charcoal oxidizes an aqueous solution of oxalic acid and several amino acids. This charcoal always contained iron. The oxidizable substance was always adsorbed and it is possible that the combination of adsorption and the presence of iron is necessary in the process. It is well known that substances adsorbed to platinum black in the presence of oxygen are oxidized rapidly. Possibly both oxygen and the oxidizable substance are brought close together by simultaneous adsorption. The speeding up of a chemical reaction by adsorption is called contact catalysis and is the principle involved in use of the combustion tube for the analysis of organic compounds, the heat applied not being sufficient to produce complete combustion. In fact, very high temperatures cause dissociation. Sulphur dioxide is oxidized by air to sulphuric acid in the presence of finely divided platinum or other contact catalysts. Ammonia is oxidized to nitric acid in the same manner. Alcohols are oxidized (dehydrogenated) to aldehydes and ketones in the same way, but in this case finely divided copper is used in preference to platinum. Oxygen and hydrogen when adsorbed to finely divided palladium or platinum unite at low temperatures. Various oxides accelerate the union of these gases when heated. This is the principle of the Welsbach gas mantle and "radiant fire" gas heaters. The union of the gases is so rapid that the flame is very small and hot. Contact catalysts are easily "poisoned" by minute quantities of some easily adsorbed substances so that they no longer function as previously. This is apparently due to the fact that the "poison" is more strongly adsorbed than the substances to be united and crowds them out of the surface.

Since one surface-active substance may crowd out another from the surface, Warburg tested the effect of anesthetics on the oxidation of substances by charcoal and found that anesthetics reduced the rate of oxidation. He also found that anesthetics reduced the activity of certain enzymes and reduced the oxidation that goes on inside of the erythrocytes, particularly the young erythrocytes with nuclei. Erythrocytes are favorable objects for study since the oxyhemoglobin furnishes a sufficient supply of oxygen to last a considerable period. The analogy between enzymes and contact catalysts is not quantitatively complete in this regard. The following table taken from Senter shows the concentrations of poisons that are effective in decreasing the action of colloidal platinum and the catalase of erythrocytes to one-half its previous value. (Numbers represent liters in which one mol was dissolved.)

Poison.	Pt.	Catalase.
H_2S	300,000	1,000,000
HCN	20,000,000	1,000,000
$HgCl_2$	2,000,000	2,000,000
$Hg(CN)_2$	200,000	3,000,000
I_2(in KI)	5,000,000	50,000
Aniline	5,000	400
HCl	3,000	100,000
NH_4Cl	200	1,000
HNO_3	no poisoning	250,000
H_2SO_4	no poisoning	50,000
KNO_3	no poisoning	40,000

Different contact catalysts may be affected differently, however, by the same poison.

It was shown by McClendon and Mitchell (1912) that those solutions that were more effective in increasing the oxidation of unfertilized sea urchin eggs were also most effective in increasing the permeability of the eggs and causing them to develop. Therefore the mechanism of the action of the anesthetic in decreasing oxidation, decreasing permeability and decreasing rate of segmentation is open to several interpretations.

CYTOLYSIS

Many substances that kill cells and many deadly physical agents, such as ultra-violet rays and x-rays, cause what is known as cytolysis. The best known instance of cytolysis is hemolysis, which is the cytolysis of the erythrocytes. In hemolysis the hemoglobin passes out of the cell and dissolves in the medium. Many other substances pass out at the same time. The evidence that ions are able to pass out is the increase in the electric conductivity of the suspension. It was shown by Czapek that various anesthetics, if used in greater amount than the anesthetic dose, caused cytolysis of plant cells when they lowered the surface tension of water to 68 per cent. of its former value. Czapek did not use the term "cytolysis." It was evident, however, that the cells were killed and Czapek found that tannin diffused out of the cells.

We interpret this outward diffusion as being a case of cytolysis. The presence of the cellulose cell wall prevented the entire disruption of the cell which occurs in the cytolysis of some animal cells.

Other writers have found that cytolysis produced by surface-active substances is proportional to the lowering of the surface tension of water by these substances. The cytolytic action of phenol, the cresols and related substances is greater, however, than would be expected from the surface activity. Many metals (cations) have a cytolytic action. The toxicity increases nearly in the order of their arrangement in the table of electrolytic solution tension. Some ions, however, are toxic and do not cytolyze under all conditions. Höber (1908) found the ionic series for the anions to be in the following order of increasing hemolytic power:

$$SO_4 < Cl < Br < NO_3 < CNS < I$$

and for the cations

$$Na < Li < Cs < Rb < K$$

Lillie (1909) observed the same anionic series for the cytolysis of sea urchin eggs. It has been found by Larson and his collaborators that soaps are extremely toxic to bacteria but that the presence of calcium ions or the formation of insoluble calcium soaps prevents the action of the soap. He also found that treatment with soap makes bacteria harmless in producing disease and also prevents the activity of certain bacterial toxins.

AMEBOID MOTION

Quincke's studies of the movements of drops of fluid due to local reduction of surface tension are probably known to the reader. Rhumbler made many models of amœbæ. In order to increase the viscosity of the oil drops he emulsified the oil with aqueous solutions. That is to say, he made emulsions of water in oil and immersed pieces of these emulsions in water. Some of them were made by grinding sodium carbonate with rancid olive oil, the soap formed being the emulsifying agent. Enough water was absorbed through the oil to dissolve some of the sodium carbonate. This emulsion tended to reverse, that is to say, form an oil-in-water type. At any rate the little droplets of sodium carbonate solution that came near the surface would burst into the water. When one burst it would produce a local lowering of the surface tension of the artificial amœba and cause the protrusion of a pseudopodium. In this way the amœba would go on moving around until all of the sodium carbonate was extruded. Rhumbler made many models of amœbæ and, by combinations of changes in surface tension with adhesions to the substratum and to food particles, imitated all forms of ameboid motion with which he was acquainted. A chloroform drop immersed in water would not take in glass splinters but would greedily "eat" splinters of shellac. If a glass splinter was coated with shellac and presented to the artificial amœba it would instantly engulf it. The glass would remain inside of the amœba until the shellac was dissolved off by the chloroform. The amœba would then eject the glass thus imitating the process of defecation.

Rhumbler found that if chloroform was mixed with powdered glass and dropped into water, the glass would be ejected by the chloroform and form a layer on its surface. In this way models of the shells of kinds of amœba known as Difflugia could be imitated. These shells had considerable rigidity. The only force that held the glass together was surface tension of the oil-water surface.

Rhumbler's experiment with artificial Difflugia demonstrates the process postulated by Harkins as taking place when an emulsifying agent stabilizes an emulsion. (See Adsorption, Chapter V.) According to Harkins a single layer of molecules of the emulsifying agent forms on the surface of the droplets of the emulsion and the molecules are oriented so that the end of the molecule that is more strongly attracted by the water, or more polar (carboxyl group), faces the water and the other end (CH_3 group) faces the oil. He supposes that some molecules are cone-shaped, that is to say, bigger at one end than the other. If the large end faces the water, an emulsion of oil in water is formed, but if the large end faces the oil, an emulsion of water in oil results. The question arises: In the living amœba what conditions affect its surface tension? It was shown by McClendon that the surface of an amœba appears to be capable of transmitting a sensation just as in the case of the irritable elements. We should therefore suppose it to be semipermeable and capable of changing its permeability just as in the case of muscle and nerve. Such a change in permeability should result in alteration of its surface tension, because the unstimulated cell is electrically polarized. Increase in permeability brings about depolarization. Hence, since polarization decreases surface tension, a local increase in permeability of the amœba would cause a local increase in the surface tension. The advancing end of a pseudopodium would therefore be a region of decreased permeability. The effect of polarization on surface tension is well shown in the capillary electrometer.

It is not supposed that surface tension explains all forms of ameboid motion as was once thought by Rhumbler. Edmund Montgomery in 1878 advanced the idea that gelation and solation or the swelling and shrinking of gels are factors in amœboid movements. More recently, Chambers by micro-dissection methods has shown that whereas the ectosarc of the general surface of an ambœa is a more or less stiff gel, the surface of the advancing pseudopodium is fluid, perhaps just as fluid as the endosarc. He also asserts that there is a solid but elastic pellicle covering the whole amœba and that the movement takes place inside this pellicle.

The contractile vacuole seems to function as a kidney for the removal of water and other substances from the amœba. Hartog has shown that it occurs in all fresh water amœbæ, which absorb water continually, but it may be absent in parasitic and marine forms, the osmotic pressure of the medium preventing the absorption of water. Rhumbler made a model of the contractile vacuole by taking a drop of impure chloroform and immersing it under water. The hydrochloric acid and alcohol in the chloroform absorbed water which separated out in the form of droplets. These droplets fused to form one which burst.

CELL DIVISION

In 1902 E. P. Lyon showed that sea urchin eggs are more susceptible to KCN during cell division than at other times. It was shown by Warburg that respiration increased preparatory to and during the first division. It has been shown in Chapter XIII that the permeability increases at this period. Viscosity and surface tension changes will be considered below. The relation between these phenomena is a matter of speculation.

Cell division usually follows the division of the nucleus. It has been shown by various observers and especially emphasized by Heilbrunn that the viscosity of the cytoplasm increases on nuclear division. Chambers has, however, differentiated between the general cytoplasm and the hyaline substance of the astral rays, the latter being fluid. It was shown by McClendon that nuclear division is not necessary for cell division.

Butschli, Rhumbler and others considered cell division to be caused by local changes in surface tension, polar regions being areas of relatively low surface tension. When the tension of a surface is locally reduced, surface currents pass away from this region toward regions of higher tension. In the case of water wetting a glass plate, a local lowering of the surface tension causes the water to flow away from this point; but when the surface tension of a free drop is lowered locally, surface currents flow away from this region and axial currents flow toward it and cause the surface to bulge out. Gardiner (1897) observed superficial granules in certain dividing eggs to pass from the polar regions toward the equator. This process was observed in the egg of Arbacia by McClendon (1910). Conklin in 1908 observed similar movements in the eggs of Crepidula. McClendon attempted to make a model of a dividing cell by adding one part of chloroform to 2 parts of rancid olive oil and immersing it in water with a layer of concentrated salt solution under it to prevent it from touching the bottom. The surface tension was simultaneously lowered at two opposite poles by squirting on it 0.1 N alkali. The drop bulged at the poles and constricted in the middle and was broken into 2 drops. This process was so rapid that it was difficult to follow with the eye. Spek (1918) used rape seed oil and in this case, owing to the viscosity of the oil, the process was slower and a beautiful division of a drop into two could be produced. In the division of plant cells, apparently a change in viscosity plays the chief role. In many of these no furrow occurs but a wall of more solid protoplasm is built up separating the two cells.

MUSCLE CONTRACTION

It was shown by Engelmann (1893) that a catgut stretched in water would contract on the addition of acid. This works only if the catgut is stretched or twisted and dried in this condition of tension; otherwise the addition of acid, which causes swelling in all directions, will result in elongation. Meigs in numerous papers has investigated the contraction of muscle and seems inclined to the swelling hypothesis.

Von Furth considers death rigor to be a form of contraction, and it is well known that lactic acid, which is associated with muscle contraction, is formed in death rigor. Fletcher and Hopkins in 1907 measured the production of lactic acid. If oxygen is excluded, lactic acid accumulates during stimulation of the muscle; that is to say, it is produced during the contractions. According to the swelling theory it is the cause of the swelling.

MacDougal (1908) supposed that swelling is due to osmotic pressure. He placed a number of metal rings on a rubber tube, and pumped up the tube. On being pumped up it shortened. Bernstein in 1901 assumed that increase in surface tension caused the contraction of muscle. Since electrical depolarization causes increase in surface tension, the contraction would then follow from the stimulation. Bernstein in 1908 observed that the temperature coefficient of muscular contraction as well as surface tension is negative, whereas for the swelling of colloids it is positive. He maintained in 1915 that unless the violin strings are twisted, they do not contract. Lillie supposes the increase of surface tension to cause aggregation of the colloidal particles, in other words, gel formation or coagulation.

According to Hill, muscle contraction cannot be due to change of surface tension by adsorption of lactic acid on a surface since the lactic acid produced by 1 cm. of muscle exerting a force of 1 dyne, is 10^{11} molecules and could cover a space of only $\frac{1}{4000}$ sq. cm. to the depth of one molecule. Since the surface is 1 cm. long, it can be equivalent to only $\frac{1}{4000}$ cm. broad and yet exerts a force of 1 dyne. This would require a difference in surface tension of 4000 dynes cm., which is unattainable.

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